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Economic Evaluation

Discrete Event Simulation to Incorporate Infusion Wait-Time When Assessing Cost-Effectiveness of a Chimeric-Antigen Receptor T Cell Therapy

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ABSTRACT

Objectives: The main objective was to use discrete event simulation to model the impact of wait-time, defined as the time between leukapheresis and chimeric antigen receptor (CAR-T) infusion, when assessing the cost-effectiveness of tisagenlecleucel in young patients with relapsed/refractory acute lymphoblastic leukemia.

Methods: The movement of patients through the model was determined by parametric time-to-event distributions, with the competing risk of an event determining the costs and quality-adjusted life-years (QALYs) assigned. Cost-effectiveness was expressed using the incremental cost-effectiveness ratio (ICER) for tisagenlecleucel compared with chemotherapy over the lifetime.

Results: The base case generated a total of 5.79 QALYs and $622 872 for tisagenlecleucel and 1.19 QALYs and $181 219 for blinatumomab, resulting in an ICER of $96 074 per QALY. An increase in mean CAR-T wait-time to 6.20 months reduced the benefit and costs of tisagenlecleucel to 2.78 QALYs and $294 478 because of fewer patients proceeding to infusion, reducing the ICER to $71 112 per QALY. Alternatively, when the cost of tisagenlecleucel was assigned pre-infusion in sensitivity analysis, the ICER increased with increasing wait-time.

Conclusions: Under a payment arrangement where CAR-T cost is incurred post-infusion, the loss of benefit to patients is not reflected in the ICER. This may be misguiding to decision makers, where cost-effectiveness ratios are used to guide resource allocation. discrete event simulation is an important tool for economic modeling of CAR-T as it is amenable to capturing the impact of wait-time, facilitating better understanding of factors affecting service delivery and consequently informed decision making to deliver faster access to CAR-T for patients.

Keywords: chimeric antigen-receptor T cell therapy, cost-effectiveness, discrete event simulation.

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Introduction

The pathway for administration of chimeric-antigen receptor T cell therapy (CAR-T) is complex relative to alternative medicines. Each dose is unique to the individual, requiring collection of the patients' white blood cells through a process called leukapheresis, followed by T cell extraction.[1] The extracted T cells are frozen and transported to a manufacturing facility for genetic modification to express chimeric antigen receptors that recognize antigen present on cancer cells.[2] The modified T cells undergo an expansion process to increase the number of cells before being transported to the clinic for infusion. This process is universal across countries and manufacturing sites. In children and young adults with relapsed or refractory acute lymphoblastic leukemia (r/r ALL), the median manufacturing time for CAR-T cells was 1.48 months (range, 0.99 to 3.45).[3]

Strict regulatory standards for processing gene-modified cellular products have encouraged companies to adopt a centralized model for manufacturing, creating an access barrier as cells must be transported to these sites.[4,5] CAR-T is routinely given in the inpatient setting, which means access to treatment may be delayed if the patient is not close to a specialist hospital.[5] There is also the risk of manufacturing failure due to poor quality or low volume of T cells.[6] Young ALL patients who have failed multiple treatment options have a very poor prognosis,[7] consequently an increase in CAR-T wait-time may result in disease progression, adverse events (AEs) or patients succumbing to their disease.[5] Additionally, higher tumor burden has been associated with worse CAR-T outcomes in young patients with ALL.[8,9] Therefore, the implication of a delay in manufacturing time is a substantial loss of benefit to patients.

Previous economic models for CAR-T submitted to health technology assessment (HTA) agencies used decision-tree structures followed by partitioned survival models to capture the impact on costs and benefits of patients not proceeding to

infusion.[10,11] Although this may be an appropriate modeling technique to ensure infused and noninfused patients are captured in the overall measure of cost-effectiveness, this approach does not provide the flexibility to test the impact of wait-time. The importance of incorporating wait-time in assessing cost-effectiveness of personalized medicines has been highlighted previously; waiting periods may affect outcomes, especially in conditions with high short-term morbidity and mortality.[12]

Discrete event simulation (DES) has been proposed as a more flexible technique to depict complex clinical pathways and capture capacity constraints, such as delays in delivery time due to waiting or queuing.[13-16] A core feature of DES is its continuous measure of time allowing the incorporation of time-varying events, which would otherwise require use of tunnel states in cohort models, and individual patient attributes, with each patient following a unique pathway through the model.[14,17] In healthcare research, DES has frequently been applied to modeling healthcare systems in which capacity constraints need to be explicitly considered or modeling of disease progression in cases which subsequent treatments impact costs and outcomes.[18]

A previous study by Tully et al[19] used DES to model the impact of CAR-T wait-time on 1-year mortality in adults with r/r diffuse large B-cell lymphoma (DLBCL) using survival data for salvage chemotherapy to estimate mortality risk over the wait-time period. Their analysis demonstrated an increase in wait-time from 0 to between 1 to 9 months corresponded to an increase in the relative mortality rate of 6% to 125% over the same time.[19] This study builds on that previous research to assess the impact of CAR-T wait-time on lifetime benefit and costs in young r/r ALL patients, measured in terms of cost per quality-adjusted life-years (QALYs). The objective of this study was to incorporate CAR-T wait-time using pre-infusion survival estimates for standard chemotherapy in a young r/r ALL population in an Australian healthcare setting. Tisagenlecleucel for r/r ALL was previously considered cost-effective by the Australian Medical Services Advisory Committee (MSAC) at an ICER range of ($69 280-$98 450 per QALY [92 373-131 267 Australian dollars]).[20] To our knowledge, this is the first analysis to capture wait-time in an economic evaluation for CAR-T.

Methods

Population, Intervention, and Comparator

Data were sourced from phase II, single-arm, multicenter studies, ELIANA[3] and ENSIGN,[21] of tisagenlecleucel in children and young adults (3-23 years of age) with ALL who had relapsed or were refractory to multiple lines of prior treatment, including possible allogeneic stem cell transplant (SCT). Treatment with CAR-T was considered from the point of leukapheresis, and wait-time was defined as the period between leukapheresis and a single infusion of tisagenlecleucel. During this period, patients may receive bridging chemotherapy to reduce or stabilize tumor burden.[22,23] The comparator was blinatumomab, considered the standard of care before the availability of tisagenlecleucel by the MSAC in Australia,[24] as well as the main comparator for the economic modeling by the UK's National Institute for Health and Care Excellence.[25] Blinatumomab is administered on an inpatient basis over a 28-day treatment cycle, and patients receive up to 5 cycles of treatment.[26] Data for blinatumomab were sourced from a published single-arm phase I/II study in young patients with r/r ALL.[7]

Model Structure

A DES model was developed in Treeage Pro 2022, Williamstown, MA. DES is a time-to-event model whereby the movement of individual patients through the model is determined by the probability of experiencing an event, randomly drawn from parametric time-to-event distributions, with the competing risk of each event determining the type of event to which costs and QALYs are assigned.[27,28]

Patients eligible for tisagenlecleucel entered the model at the point of leukapheresis. After leukapheresis, patients could experience a pre-infusion AE, death, or proceed to successful infusion, as competing events during the wait-time period. Those who experienced a pre-infusion AE were assumed too unwell to receive CAR-T and were treated with the comparator. The chance of manufacturing failure was not considered a time-dependent variable as a chance node based on the probability of manufacturing failure from ELIANA[3] (Fig. 1 and Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008). If manufacturing was not successful, patients reentered the model, providing another opportunity to proceed to successful infusion. This was considered to reflect clinical practice where manufacturing may be repeated. Given that not all patients may be able to wait for cells to be re-manufactured, we tested the impact of removing the ability for patients to reenter the model in sensitivity analysis.

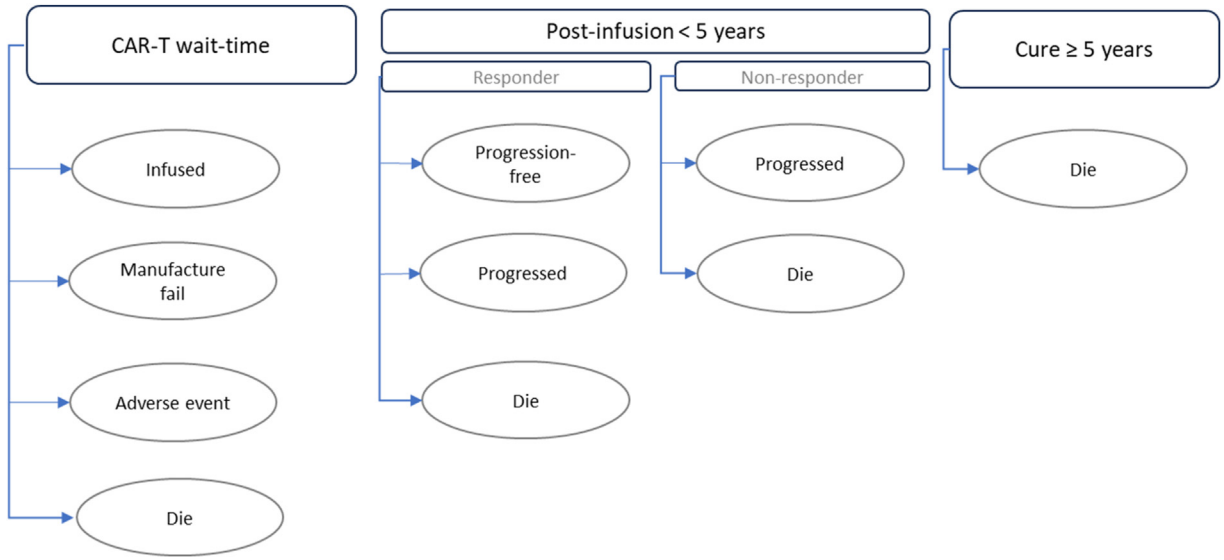
The model was structured to accommodate an outcomes-based payment arrangement, based on patients achieving a clinical response at 3 months, following the approach applied in a previous model for tisagenlecleucel in r/r ALL.[11] Responders moved to the progression-free survival (PFS) health state, with the option to receive subsequent SCT, in which they remained until they experienced a progression event or death. Non-responders moved to a progressive disease (PD) health state in which they remained until death. Responders who experienced a progression event moved to a responder PD state. Patients who remained alive at 5 years (cure point) moved to a long-term survival health state where time-varying probabilities were applied from general population mortality using Australian life-tables[29] adjusted by a standardized mortality ratio (SMR) of 9.05 based on a Canadian cohort study in childhood cancer patients that demonstrated mortality risk was greatest for patients whose disease had recurred within 5 years of diagnosis.[30] Previous economic evaluations for tisagenlecleucel in ALL considered by HTA agencies have applied cure-points between 2 to 5 years.[20] SMR adjusted general population mortality data were linked to individual patient age using bootstrapping.

For the blinatumomab arm of the model, patients entered the PFS health state where they remained until progression or death. On progression, patients moved to the progression health state until death. Patients alive at 5 years moved to a long-term survival health state, following the same approach as for tisagenlecleucel. In the blinatumomab study,[7] 34% of patients proceeded to SCT, and these patients are included in the overall survival (OS) data, consequently the benefit of patients proceeding to SCT is captured for blinatumomab.

Time-to-event Distributions

Data for the ELIANA and ENSIGN studies were pooled to derive time-to-event distributions, supported by visual inspection of the OS Kaplan-Meier (KM) curves and no statistically significant difference in OS between the studies (hazard ratio [HR] 0.62, 95% CI 0.36-1.0; P = .098). Pre-infusion wait-time was calculated from pooled individual data from ELIANA and ENSIGN, estimated from the date of enrolment to date of infusion. Date of enrolment in the trials occurred after leukapheresis and acceptance of cell product, thus actual wait-time may be underestimated. Mean wait-time for patients (N = 143) was 1.55 months from enrolment to infusion, with a minimum and maximum wait-time of 0.39 and 3.81

Figure 1. Discrete event simulation model structure.



months (Appendix Fig. 2A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008).

OS for patients receiving bridging chemotherapy was derived from a retrospective analysis of outcomes for salvage chemotherapy in children and young adults with relapsed ALL,[31] reconstructed from the published KM OS curve following the approach by Guyot et al[32] 2012 and implemented using the statistical software R *IPDfromKM* package version 0.1.10.[33] The "curative intent" treatment group from this study was selected because this group was considered to represent patients eligible for CAR-T.

The risk of patients experiencing a pre-infusion AE was derived from the proportion of enrolled patients in ELIANA who did not proceed to CAR-T infusion because of an AE. Patients not proceeding to CAR-T because of an AE were assumed to receive treatment with blinatumomab and assigned the corresponding costs and benefits. To estimate the time-to-event for pre-infusion AEs, an exponential distribution was applied, and the rate

Figure 2. Kaplan-Meier survival curves for responder progression-free survival (RspPFS), responder progressive disease (RspPPS) and non-responder overall survival (NRspOS).

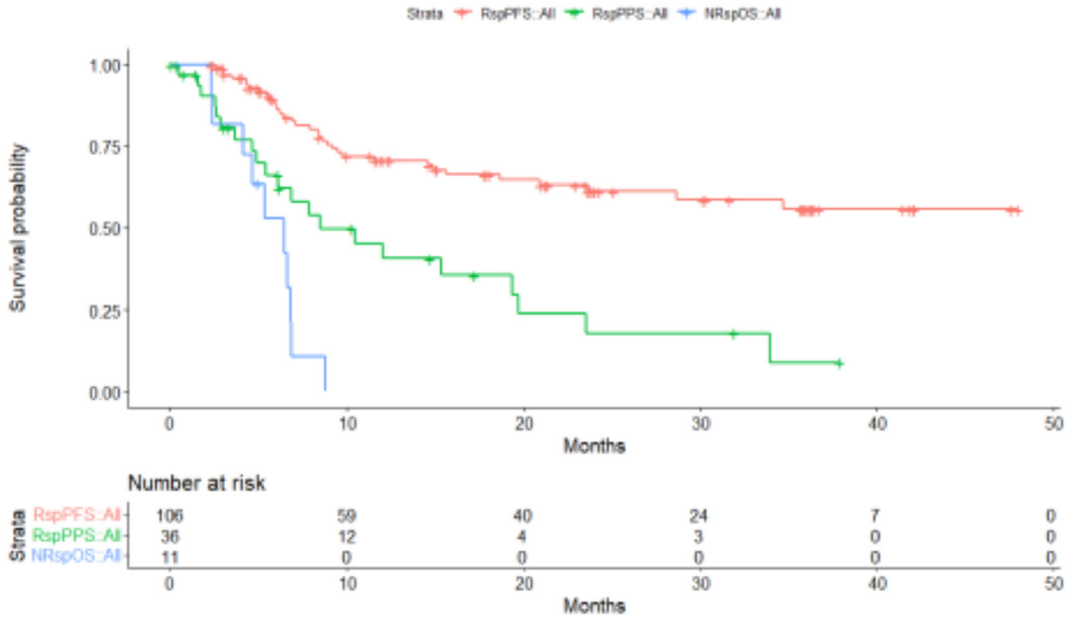


Table 1. Key base case and sensitivity input parameters.

Tisagenlecleucel			
Pre-infusion distributions	Selected	Parameters	Source
CAR-T wait-time	Lognormal	μ = 0.338	Pooled ELIANA[3] and ENSIGN[21]
		σ = 0.373	
Pre-infusion AEs*	Exponential	λ = 0.021	ELIANA[3]
Pre-infusion OS	Lognormal	μ = 1.611	Von Stackelberg[31]
		σ = 0.828	
Post-infusion distributions	Selected	Parameters	Source
Responder PFS	Lognormal	μ = 3.594	Pooled ELIANA[3] and ENSIGN[21]
		σ = 1.431	
Responder PD	Exponential	λ = 0.063	
Non-responder PD	Gompertz	λ = 0.536	
		γ = 0.018	
Pre-infusion probabilities*	Base	Sensitivity (range)	Source
Manufacturing failure	0.08	0, 0.1	ELIANA[3]
Adverse event	0.03	-	
Death	0.08	-	
Response probabilities*	Base	Sensitivity (range)	Source
Responders†	0.81	0.65, 0.97	Pooled ELIANA[3] and ENSIGN[21]
Subsequent SCT‡	0.22	0, 0.30	
Non-response	0.08	Correlated	
Dead	0.09	Correlated	
Lost to follow-up	0.02	Correlated	
Other important parameters	Base	Sensitivity (range)	Source
Mean CAR-T wait-time, months	1.55	0.00, 6.20	Pooled ELIANA[3] and ENSIGN[21]
"Cure point," years§	5	2, 10	MacArthur[30]
Long-term SMR	9.05	-	
CAR-T cost on infusion‖	$375 000	-	NICE[25]
CAR-T cost on leukapheresis	-	$375 000	
Blinatumomab			
Distributions	Selected	Parameters	Source
OS	Lognormal	μ = 1.78	Von Stackelberg[7]
		σ = 1.308	
Other parameters	Base	Sensitivity (range)	Source
HR PFS:OS	0.83	-	Parker[35]
Pricing	$49 080	-	PBS[38]
Tisagenlecleucel and blinatumomab			
Utility and disutility values¶	Base	Sensitivity (range)	Source
Pre-infusion PD	0.65	-	ELIANA[3]
PFS PD	0.81 0.69	0.74, 0.88 0.60, 0.78	
Grade 3/4 CRS	−0.8	-	Assumption
Other SAEs	−0.1	-	Casado[39]
Subsequent SCT	−0.57	-	Sung[40]
Other parameters	Base	Sensitivity (range)	Source

continued on next page

Table 1. Continued

Tisagenlecleucel			
Discount rate, %	5.0	-	MSAC[41]
SCT cost	$218 021	-	Gordon[42]

AE indicates adverse event; CAR-T, chimeric-antigen receptor T cell therapy; CRS, cytokine release syndrome; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; OS indicates overall survival; PD, progressive disease; PFS, progression-free survival; SAE, serious adverse event; SCT, stem cell transplant; SMR, standardized mortality ratio; USD, US dollar.
*Sourced from ELIANA only due to differences in reporting of patient disposition of the enrolled set.
†As a proportion of the infused population from ELIANA.
‡The proportion of patients who had undergone SCT at 12-months as a proportion of responders.
§"Cure point" was assumed at 5 years; whereby all-cause mortality was adjusted by an SMR of 9.05 based on a Canadian cohort study in childhood cancer patients who had survived at least 5 years.
‖A published price for tisagenlecleucel was not available in Australia, therefore a price of 375 000 USD was.
¶Quality of life data not captured in ENSIGN assumed, based on the NICE published price.

parameter was calculated[34] using the mean wait-time for tisagenlecleucel.

Post-infusion Distributions

Post-infusion PFS and OS distributions were estimated from the pooled tisagenlecleucel trial data using event-free survival (EFS) and OS time-to-event data (Fig. 2). EFS was measured from the time of first tisagenlecleucel infusion to relapse, death due to any cause, or treatment failure and was considered representative of PFS whereby patients either remained in PFS, progressed, or died. OS was measured from the time of first tisagenlecleucel infusion to the time of death due to any cause. Time in PFS for responders at 3 months was estimated from EFS data for patients who achieved a clinical response at 3 months. Time in PD was estimated from the OS data for nonresponders at 3 months. For responders who progressed, time in PD was estimated from analysis of OS data for patients who had responded at 3 months and then lost response or progressed. Background mortality for responders in PFS was taken into account by applying the SMR adjusted time-varying probabilities from Australian life tables.[29] This was to account for deaths due to all-cause mortality while in PFS. Further details of the analysis of individual data are provided in the Appendix Text in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008.

Blinatumomab

For blinatumomab, time in PFS was estimated by reconstructing individual data from the published KM OS curve,[7] adjusted by a HR of 0.83 between OS and EFS, based on the relationship observed between OS and EFS KM curves from a study of mitoxantrone in pediatric ALL.[35] This assumption was tested in a previous economic evaluation by varying the HR between 0.76 to 0.99 and had minimal impact on the results.[11] Time-to-event data for blinatumomab patients moving from PFS to PD were not available; therefore, the distribution for nonresponders to tisagenlecleucel was applied.

The software R, Statistical Computing 2021 with the flexsurvreg package version 2.2[36] and STATA 17, StataCorp 2021 were used for the data analysis. Selection of the type of parametric distribution was based on whether the model was statistically a good fit according to the joint lowest Akaike information criterion and Bayesian information criterion, and whether the distribution was clinically and biologically plausible[37] (Appendix Fig. 3). The selected distributions are described in Table 1.[21,25,30,31,35,38-42]

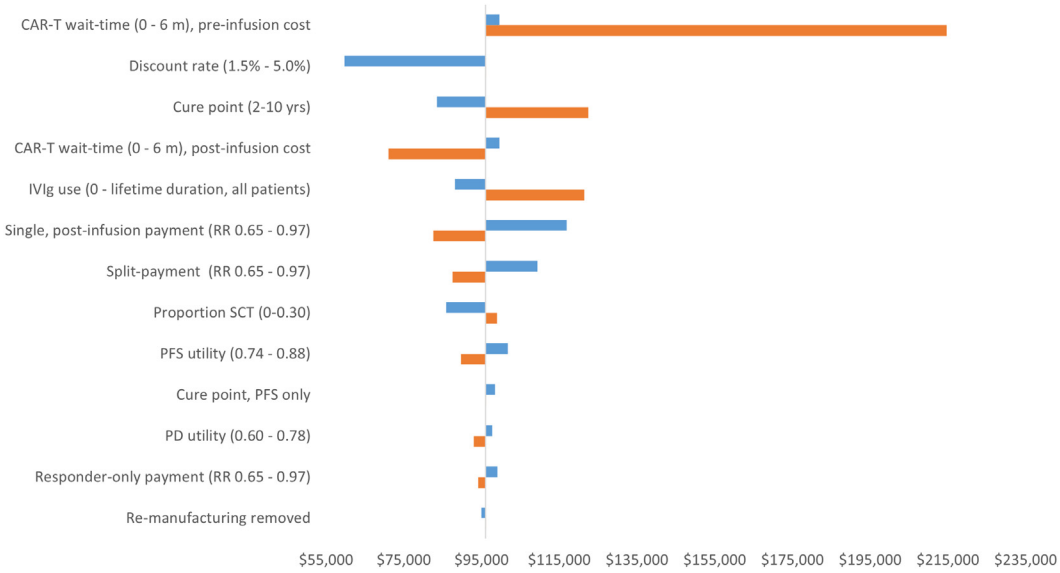
Utilities

Utility values were calculated from patient-level EQ-5D-3L data from the ELIANA study, updated from previous values with a more recent data-cut, using UK preference weights[43] for patients aged 13 years and above. An implicit assumption is that EQ-5D data for patients above 13 years were applicable to those under 12 years and under. The PD state included EQ-5D assessments before infusion of tisagenlecleucel and after a PFS event, combined into a single PD utility value (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008). Utility data for patients before infusion with tisagenlecleucel was applied to the pre-infusion period in the model. For blinatumomab, no published utility data were available; therefore, the tisagenlecleucel values were used. A one-off disutility was applied to each treatment arm to capture the loss of quality of life due to severe AEs, including grade 3/4 cytokine release syndrome (CRS), other serious AEs (SAEs), and subsequent SCT.[39,40] Utilities used in the model are summarized in Table 1.[21,25,30,31,35,38-42]

Costs

Costs were estimated from an Australian healthcare system perspective, consistent with MSAC Guidelines.[41] Cost inputs sourced from prior publications were adjusted for inflation using the RBA's inflation calculator[44] and when sourced from international publications, converted to Australian dollars using RBA exchange rates.[45] For the purposes of publication, costs are reported in US dollars.[46] The cost for tisagenlecleucel was applied post-successful infusion in the base-case at a cost of USD 375 000 based on the National Institute for Health and Care Excellence published price[25] because the Australian price was not publicly available. The cost per course of blinatumomab was calculated using the Australian Pharmaceutical Benefits Scheme (PBS) price[38] as USD 49 080 (AUD 65 502) and a mean number of treatment cycles from the clinical study,[7] noting that the net price may be lower because of confidential pricing arrangements. Costs associated with the administration of each treatment were also included. Other costs included subsequent SCT,[42] management of SAEs, including use of tocilizumab for CRS and intravenous immunoglobulin (IVIg) for B-cell aplasia, and routine disease management costs, which varied depending on whether the patient was progression-free or their disease had progressed. Detailed methods of calculating costs have been published previously.[11]

Figure 3. Tornado diagrams showing impact of parameters varied in sensitivity analyses on the incremental cost-effectiveness ratio. Blue bars indicate the lowest parameter from the base case and red bars indicate the highest parameter value from the base case.



IVIg indicates immunoglobulin; m, months; PFS, progression-free survival; PD, progressive disease; SCT, allogenic stem cell transplant.

Model Simulation

Long-term modeled benefits were measured in terms of life-years (LYs) and QALYs. Events continued to occur until no patient remained alive in the model, with the last patient exiting the model after 89 years. A total of 10 000 patient simulations were run, set to 1000 simulations when multiple sensitivity analyses were performed because of processing time. Costs and outcomes were discounted at a rate of 5%, as recommended by MSAC Guidelines.[41] Total costs and QALYs were calculated as the time spent in each health state multiplied by the costs and utilities assigned to each health state. The threshold for cost-effectiveness was set at USD 98 450 per QALY based on the upper range previously reported to be considered cost-effective by MSAC for tisagenlecleucel in r/r ALL,[20] noting that Australia has no explicit ICER threshold for cost-effectiveness and that the recommendation was conditional on a risk-share arrangement.[41,47]

CAR-T Wait-Time

Real-world data from the Center for International Blood and Marrow Transplant Research for ALL patients reported a median wait-time of 33 days (range, 21-91). A median wait-time of 6 months (range, 2-8 months) was reported for another CAR-T, idecabtagene vicleucel, in multiple myeloma.[48] We tested the impact of CAR-T wait-time on cost-effectiveness by multiplying the wait-time distribution by a factor of 0 to 4, effectively varying mean CAR-T wait-time between 0 and 6.2 months to represent lower and upper bounds that could occur in clinical practice. Additionally, we looked at the impact of incurring the cost of CAR-T pre-infusion to determine how the timing of the payment affected cost-effectiveness under varying wait-times.

Additional Sensitivity Analyses

One-way sensitivity analyses were performed on IVIg use and duration and proportion of patients who received subsequent SCT and changes to the cure point because these were identified as key sources of uncertainty in HTA reviews.[20] Discount rate was tested because of the potential impact the discount rate can have on a therapy with a single, upfront cost and potential lifetime benefit.[49] The model was structured to incorporate an outcomes-based payment arrangement, allowing for the impact of different payment structures to be tested by varying response rates (further described in Appendix Section in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008). Considering the lack of utility data in patients under 13 years, sensitivity analysis was performed on PFS and PD utility values. We also tested the impact of applying the cure-point assumption to patients in PFS only, rather than applying SMR adjusted all-cause mortality to the entire population alive at 5 years, as well as removing the ability for patients to reenter the model following manufacture failure.

Results

Base Case

The model base case generated 7.43 LYs and 5.79 QALYs for tisagenlecleucel compared with 1.75 LYs and 1.19 QALYs for blinatumomab, generating costs of $622 872 for tisagenlecleucel and $181 219 for blinatumomab, resulting in ICER of $96 074 per QALY. Over the wait-time period, the simulated proportion of patients who experienced manufacturing failure, AEs and death in the model aligned with the ELIANA trial (0.08, 0.03, and 0.08, respectively [Table 1[21,25,30,31,35,38-42] and Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008]), validating the model simulation was consistent with the clinical trial data at the pre-infusion phase.

CAR-T Wait-Time

In sensitivity analysis, setting wait-time to 0 increased the benefit of CAR-T from a base case of 5.79 to 6.30 total QALYs, whereas increasing wait-time to 6.2 months reduced the benefit of CAR-T to 2.78 total QALYs (Fig. 3 and Table 2). The large reduction in QALYs at 6.2 months for CAR-T reflects the poor survival outcomes for patients treated with salvage chemotherapy

Table 2. Costs, QALYs and ICERs for tisagenlecleucel versus blinatumomab at different wait times, when CAR-T cost is applied post-infusion versus pre-infusion.

Wait time	Tisagenlecleucel			Blinatumomab			Incremental	
	Cost, $	LYs	QALYs	Cost, $	LYs	QALYs	Cost/LY, %	Cost/QALY, $
Zero wait-time								
Post-infusion payment	689 569	8.19	6.30	181 219	1.75	1.19	78 929	99 602
Pre-infusion payment	689 569	8.19	6.30	181 219	1.75	1.19	78 929	99 602
1.6 months wait-time								
Post-infusion payment*	**622 872**	**7.43**	**5.79**	**181 219**	**1.75**	**1.19**	**77 729**	**96 074**
Pre-infusion payment	663 908	7.43	5.79	181 219	1.75	1.19	84 951	105 001
3.1 months wait-time								
Post-infusion payment	497 173	5.90	4.66	181 219	1.75	1.19	76 177	91 076
Pre-infusion payment	612 054	5.90	4.66	181 219	1.75	1.19	103 875	124 192
4.7 months wait-time								
Post-infusion payment	377 369	4.40	3.55	181 219	1.75	1.19	73 914	83 030
Pre-infusion payment	559 321	4.40	3.55	181 219	1.75	1.19	142 479	160 050
6.2 months wait-time								
Post-infusion payment	294 478	3.36	2.78	181 219	1.75	1.19	70 172	71 112
Pre-infusion payment	523 112	3.36	2.78	181 219	1.75	1.19	211 827	214 664

Note. Boldface indicates base-case results.
ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
*Base-case analysis results.

(median OS of 4 months[31]; Appendix Figure 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008).

Costs for tisagenlecleucel were also sensitive to wait-time, with 0 wait-time resulting in an increase in the costs for tisagenlecleucel to $689 569 because of more patients proceeding to infusion, whereas an increase in wait-time had the reverse impact on costs, reducing costs for tisagenlecleucel to $294 478 because of fewer patients proceeding to infusion (Table 2).

Consequently, when the cost of tisagenlecleucel was incurred post-infusion, wait-time had an inverse relationship on cost-effectiveness, reducing the ICER to $71 112 when wait-time was extended to 6.2 months (Fig. 3 and Table 2). Alternatively, when the cost of tisagenlecleucel was incurred pre-infusion, extended wait-time had the reverse impact on the ICER, with cost per QALY increasing to $214 664 at 6.2 months wait-time.

Additional Sensitivity Analyses

The ICER was sensitive to discount rate, with a reduction in the discount rate to 1.5% reducing the cost per QALY to $59 769. Other variables that had a substantial impact on cost-effectiveness included: extending the cure point to 10 years, applying a lifetime duration of IVIg use to all patients, and increasing or decreasing the response rate at 3 months when a single, post-infusion payment was applied (Fig. 3 and Table 3).

Discussion

The main advantage of using DES to model the cost-effectiveness of CAR-T was the ability to capture the administration process, from the point of leukapheresis to CAR-T infusion. In modeling this process, we have shown that extended wait-time has a substantial impact on the benefit of CAR-T at a population level. When wait-time increased to approximately 6 months, the mean QALY loss was 3.51 per patient over a lifetime compared with 0 wait-time. The substantial loss in QALYs with increasing wait-time was due to the high mortality risk for patients while receiving bridging chemotherapy, based on the survival curve for chemotherapy in young patients who had not responded to salvage chemotherapy and treated with intensive poly-chemotherapies and SCT.[31]

Despite the large QALY loss with increasing wait-time, the cost-effectiveness ratio fell because of fewer patients proceeding to infusion and therefore not incurring the cost of CAR-T. However, when the cost of CAR-T was applied at the pre-infusion stage, pre-infusion, extended wait-time resulted in an increase in the ICER because the cost of infusion was incurred regardless of a successful infusion. A sensitivity analysis was conducted that incorporated a pre-infusion payment as a means of assessing the robustness of the model results to the timing of the initial payment, not as a solution for incentivizing faster delivery of CAR-T (because payment for patients who do not proceed to infusion would increase the financial impact of CAR-T on healthcare system, without commensurate health gains). The results of that analysis indicate that timing of payments affects the model results. Policy makers may wish to consider approaches tailored to awarding payment for CAR-T delivered within a pre-defined time frame, or perhaps a tiered payment arrangement, so that faster delivery times are associated with a higher payment (p.13). The use of DES allows those differences in payment structures, including differences in timing, to be captured, thereby providing a more complete assessment of their impact on the associated cost-effectiveness of CAR-T therapies.

The introduction of next generation CAR-Ts warrants the use of DES as a technique for modeling the cost-effectiveness because wait-time will be an important variable to consider in assessing the additional value, in terms of cost-effectiveness, rapid CAR-Ts may provide. The next generation of rapid CAR-Ts are expected to reduce manufacturing time to as little as 2 days, eliminating the need for T cell activation or ex vivo expansion,[50] with a phase I

Table 3. Incremental costs, QALYs and ICERs for the sensitivity analyses.

Parameter	Incr. costs	Incr. QALYs	ICER
Base case	**$441 652**	**4.60**	**$96 074**
Discount rate			
1.50%	$567 605	9.50	$59 769
Cure point			
2 years	$517 261	6.10	$83 535
10 years	$403 398	3.30	$122 514
IVIg use			
None	$405 236	4.60	$88 153
Lifetime, all patients	$558 428	4.60	$121 477
Single, post-infusion payment			
RR 0.65	$411 224	3.52	$116 957
RR 0.97	$473 798	5.73	$82 629
Split payment			
RR 0.65	$384 689	3.52	$109 410
RR 0.97	$501 777	5.73	$87 508
Proportion SCT			
0.00	$405 431	4.59	$85 892
0.30	$454 411	4.72	$98 953
PFS utility			
0.74	$441 195	4.34	$101 770
0.88	$441 195	4.92	$89 706
Proportion manufacture failure			
0	$435 613	4.58	$90 366
0.1	$442 643	4.90	$95 358
5-year cure point applied to PFS only			
Cure point, PFS only	$98 475	4.60	$98 475
PD utility			
0.6	$441 195	4.51	$97 791
0.78	$441 195	4.74	$93 043
Responder-only payment			
RR 0.65	$348 596	3.52	$99 145
RR0.97	$539 894	5.73	$94 155
Re-manufacturing removed			
No model re-entry following manufacture fail	$397 918	4.19	$94 933

Note. Boldface indicates base-case results.
CAR-T indicates chimeric-antigen receptor T cell therapy; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PD, progressive disease; PFS, progression-free survival; QALYs, quality-adjusted life-years; RR, response rate; SCT, stem cell transplant.

clinical trial underway in adults with B-cell malignancies.[46] Additionally, incorporating wait-time in an economic analysis may inform decisions on how access to current CAR-Ts is prioritized within the healthcare system by illustrating the sensitivity of cost-effectiveness to the inclusion of wait-time as a factor affecting the value of care.

Previous analyses have shown an impact of CAR-T wait-time on survival benefit.[19,51] A study looking at the impact of CAR-T wait time from a societal perspective showed QALY losses between 0.7 and 4.8 in r/r ALL when wait-time was delayed between 1 to 6 months compared with patients treated immediately.[52] In adult r/r DLBCL, an increase in wait-time from 1 to 9 months corresponded to an increase in mortality from 36.12% to 76.33%.[19] In another study, a reduction in CAR-T wait-time resulted in survival gains, with a mean of 0.27 to 0.59 QALYs gained over a 3-year period when wait-time was reduced by up to 2 months. This was attributed to more patients accessing CAR-T, as well as better post-infusion outcomes in patients because of lower tumor burden.[51] Another study used the relationship between lactate dehydrogenase (LDH) levels and tumor progression to estimate the impact of wait time on survival, estimating an additional 0.0673 life-years per patient when wait-time was reduced by 2 months, compared with the 3-year mean survival time from the tisagenlecleucel clinical trial in DLBCL(JULIET).[51] We did not find an association between wait-time and overall survival post CAR-T infusion; therefore, we did not adjust survival outcomes by wait-time in the model (Appendix Fig. 2B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.008).

We recognize the limitations of the model in terms of the noncomparative nature of the clinical evidence and limited patient follow-up in the context of a potentially curative therapy; however, the purpose of this research was to assess the sensitivity of model outcomes to changes in CAR-T wait-time; hence, the impact of heterogeneity in the data was not explored. Wait-time in the model was measured from the time of enrolment to the point of infusion, with enrolment into the trials occurring after leukapheresis and only once cells were accepted for infusion. Consequently, wait-time was likely underestimated in the base case, although this was addressed in sensitivity analysis.

Populating the model required subgroup analysis to generate survival curves by response status, as well as post-progression survival for patients who initially responded and subsequently lost response. This meant the number of patients by subgroup was small and may have generated less reliable results compared with the overall population. Lack of data for blinatumomab meant that post-progression data and utilities were derived from tisagenlecleucel, potentially affecting comparative values. Additionally, there was a lack of cost data, particularly associated with administration of CAR-T and AE management, consequently, estimates may under- or over-estimate actual costs in clinical practice. We also note our analysis required access to individual data made available to the authors by Novartis, although is not in the public domain, limiting replicability.

Conclusion

Infusion wait-time has a substantial impact on the benefit of CAR-T at a population level. Extended wait-time substantially reduced the ICER because of fewer patients proceeding to infusion resulting in less benefit but also less cost. This may be misguiding to decision makers, where cost-effectiveness ratios are used to guide resource allocation. This study highlights the importance of using DES to facilitate better understanding of the factors affecting service delivery and consequently informed decision making to deliver faster access to CAR-T for patients.

Author Disclosures

Links to the disclosure forms provided by the authors are available here.

The views expressed are those of the authors and not necessarily those of Novartis Pharmaceuticals or the Centre for Health Economics Research and Evaluation.

Supplemental Material

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