PharmacoEconomics
https://doi.org/10.1007/s40273-024-01430-7

ORIGINAL RESEARCH ARTICLE

Different Models, Same Results: Considerations When Choosing Between Approaches to Model Cost Effectiveness of Chimeric-Antigen Receptor T-Cell Therapy Versus Standard of Care

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Accepted: 18 August 2024

Abstract

Objective Chimeric antigen-receptor T-cell therapy (CAR-T) is characterised by early phase data at the time of registration, high upfront cost and a complex manufacturing and administration process compared with standard therapies. Our objective was to compare the performance of different models to assess the cost effectiveness of CAR-T using a state-transition model (STM), partitioned survival model (PSM) and discrete event simulation (DES).

Methods Individual data for tisagenlecleucel for the treatment of young patients with acute lymphoblastic leukaemia (ALL) were used to populate the models. Costs and benefits were measured over a lifetime to generate a cost per quality-adjusted life-year (QALY). Model performance was compared quantitatively on the outcomes generated and a checklist developed summarising the components captured by each model type relevant to assessing cost effectiveness of CAR-T.

Results Models generated similar results with base-case analyses ranging from an incremental cost per QALY of $96,074–$99,625. DES was the only model to specifically capture CAR-T wait time, demonstrating a substantial loss of benefit of CAR-T with increased wait time.

Conclusion Although model type did not meaningfully impact base-case results, the ability to incorporate an outcome-based payment arrangement (OBA) and wait time are important elements to consider when selecting a model for CAR-T. DES provided greater flexibility compared with STM and PSM approaches to deal with the complex manufacturing and administration process that can lead to extended wait times and substantially reduce the benefit of CAR-T. This is an important consideration when selecting a model type for CAR-T, so major drivers of uncertainty are considered in funding decisions.

1 Introduction

Chimeric antigen-receptor T-cell (CAR-T) therapies differ to other oncology medicines because they are associated with a complex manufacturing process, registration based on early phase, single-arm clinical studies and high upfront costs [1, 2]. Consequently, conventional modelling approaches may not be appropriate. Cost-effectiveness analyses of CAR-T considered by health technology assessment (HTA) agencies have relied on partitioned survival models (PSMs) to inform public funding decisions [3]. A PSM may be considered an appropriate choice over other approaches where time-to-event data are available, particularly overall survival (OS) and progression-free survival (PFS), and is the approach most commonly applied in economic models assessing the cost effectiveness of oncology medicines [4]. Within PSM, area under the curve (AUC) modelling is used to derive the proportion of patients in each health state; therefore, health states are independent of one another as the movement of patients is not determined by the relationship between disease progression and death using transition probabilities [5, 6]. The independence of the health states has been shown to increase uncertainty in long-term extrapolations of OS and PFS endpoints, as inter-related aspects of the disease process are not captured [5, 6]. This led the National Institute for Health and Care Excellence (NICE) Decision Support Unit to recommend that PSMs should be accompanied by state-transition models (STMs) to better assess the plausibility of extrapolations [5].

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Published online: 07 September 2024

Key Points for Decision Makers

The unique characteristics of chimeric antigen-receptor T-cell therapy (CAR-T) warrant exploration of alternative modelling structures for assessing cost effectiveness.

The ability to incorporate an outcome-based payment arrangement (OBA) and wait time are important elements to consider when selecting a model for CAR-T.

All three model types (state-transition model [STM], partitioned survival model [PSM] and discrete event simulation [DES]) incorporated an OBA, although changes in CAR-T wait time were only tested using DES due to the relative ease in in which more complex pathways could be modelled.

STMs include both cohort Markov models and individual patient models (known as microsimulation or Monte Carlo simulation) [7]. One advantage of microsimulation over cohort STMs is the ability to incorporate an individual's characteristics to influence their movement through different health states, which would be complicated and unwieldy using a cohort approach [5, 7]. Microsimulation STMs, however, require more computation time, a relevant consideration if probabilistic analysis is used [7]. STMs differ primarily from PSMs because the proportion of people moving between health states is determined using transition probabilities [5–7]. This means additional data are required over a conventional three-health-state PSM consisting of PFS, progressive disease (PD) and death, to estimate the transition probabilities for patients in the PD state, not usually captured in analyses of clinical trial data [5].

To date, discrete event simulation (DES) has been less commonly used as a modelling approach for cancer treatments. DES is a stochastic method where the movement of individual patients is driven by the time to an event, as opposed to STM where events are generated using probabilities applied at fixed cycle lengths [8, 9]. DES is usually applied to model complex structures and is recommended when it is important to capture the effects of capacity constraints such as delays in access due to waiting or queuing in an assessment of cost effectiveness [10, 11]. However, sourcing data to populate more complex clinical pathways captured by DES can be onerous, and there is perceived lack of transparency in how such models function, particularly if the model is built using simulation software [12].

Functionally, DES can capture the clinical pathway leading to receipt of an intervention, to estimate the effects of extended wait time in terms of costs and quality-adjusted life-years (QALYs) [12]. This is a key component to consider for CAR-T because the administration process is complicated, requiring the patient to undergo leukapheresis, followed by a wait-time period while the patient's T cells undergo genetic modification at a manufacturing facility. In children and young adults with relapsed or refractory acute lymphoblastic leukaemia (r/r ALL), the median processing time for CAR-T cells was 1.48 months (range 0.99–3.45) in the ELIANA trial [13], and is subject to variation in clinical practice [14–16].

We previously used PSM and DES to model cost effectiveness of CAR-T in young patients with r/r ALL, structuring the models to incorporate an outcome-based payment arrangement (OBA), and in the case of DES, factoring in CAR-T wait time [17, 18]. In this paper, we compare three modelling approaches, PSM, DES and STM, to assess whether model structure leads to a meaningful difference in results. This may assist in providing a framework to inform the most appropriate approach for evaluating cost effectiveness of future CAR-T therapies that could extend to other cell and gene therapies.

2 Methods

All models were designed to compare costs and benefits of CAR-T versus standard care in a young population with r/r ALL. Benefits were measured in cost per life-year (LY) and QALYs from an Australian healthcare system perspective. Costs and benefits were discounted at a rate of 5% per year, consistent with Australian Guidelines [19]. The methods reported here focus on the structure of the STM, as the PSM and DES models have been described previously [17, 18]. The main parameter inputs are summarised in Table 1. The same assumptions and inputs were applied consistently to enable comparison of the results across the model types. A detailed comparison of the model methods is provided in Table S1 (see electronic supplementary material [ESM]).

2.1 Clinical Data

All models used data sourced from two, phase II, single-arm clinical trials of the CAR-T therapy tisagenlecleucel [13, 30] in young patients (3–23 years of age) who had relapsed or were refractory to multiple lines of treatment, including possible allogeneic stem cell transplant (SCT). For the comparator, blinatumomab, data were from a published single-arm phase I/II study in a similar population of young patients with r/r ALL [22]. Access to individual patient

Table 1 Key assumptions and data sources across the different economic models

Intervention	Parameter	Source
Tisagenlecleucel		
Pre-infusion distributions		
CAR-T wait time	Lognormal (μ= 0.338, σ = 0.373)	ELIANA [13], ENSIGN [20]
Adverse event[a]	Exponential (λ = 0.021)	ELIANA [13]
Chemotherapy OS	Lognormal (μ= 1.611, σ = 0.828)	Von Stackelberg [21]
Pre-infusion probabilities[a]		
Death	0.08	ELIANA [13]
Adverse event	0.03	
Manufacturing failure	0.08	
Response probabilities[b]		
Responders	0.81	ELIANA [13], ENSIGN [20]
Subsequent SCT[c]	0.22	
Non-responders	0.08	
Dead	0.09	
Lost to follow-up	0.02	
Post-infusion distributions		
Responder PFS	Lognormal (μ= 3.594, σ = 1.431)	ELIANA [13], ENSIGN [20]
Responder PD	Exponential (λ = 0.063)	
Non-responder PD	Gompertz (λ = 0.536, γ = 0.018)	
Blinatumomab		
Survival distributions		
OS	Lognormal (μ=1.78, σ = 1.308)	Von Stackelberg [22]
PFS	HR-adjusted OS	Parker [23]
Long-term extrapolation	SMR-adjusted all-cause mortality at 5 years	MacArthur [24]
Costs		
Tisagenlecleucel (on infusion)[d]	$375,000	NICE [25]
Blinatumomab	$49,127	PBS [26]
SCT	$218,021	Gordon [27]
Utility and disutility values		
Pre-infusion PD	0.65	
PFS	0.81	ELIANA [13]
PD	0.69	Casado [28]
Grade 3/4 CRS	−0.8	Sung [29]
Other SAEs	−0.1	
Subsequent SCT	−0.57	

CAR-T chimeric antigen-receptor T-cell therapy, *CRS* cytokine release syndrome, *HR* hazard ratio, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *SAE* serious adverse event, *SCT* stem cell transplant, *SMR* standardised mortality ratio

[a]Sourced from ELIANA only due to differences in reporting of patient disposition of the enrolled set

[b]Infused population

[c]The proportion of responders who underwent SCT at the 12-month assessment point was applied in the model

[d]A published price for tisagenlecleucel is not available in Australia, therefore a price of 375,000 USD was assumed, based on the NICE published price [25]

data from the clinical trials enabled sub-group analysis to generate Kaplan-Meier (KM) survival data to inform the economic models. For blinatumomab, survival data were reconstructed from the published data [22]. Data analyses were performed using the software R, Statistical Computing 2021 and STATA 17, StataCorp 2021.

2.2 STM Structure

The model was built in Microsoft Excel® using a monthly cycle length modelled over a lifetime horizon (Fig. 1). The STM was structured to accommodate an OBA for tisagenlecleucel, using complete remission (response) at 3 months

post-infusion as the clinically relevant outcome linked to payment. The CAR-T eligible population was captured using a decision tree to follow patients from the point of leukapheresis to assessment of response at 3 months; thereafter, patients entered the STM consisting of four health states: PFS, responder PD (RspPD), non-responder PD (NRspPD) and death. Patients who did not receive an infusion, due to an adverse event or manufacturing failure, were assigned to treatment with the comparator. Treatment initiation with blinatumomab was considered from the point of infusion, hence the entire patient cohort was modelled using three health states, PFS, PD or dead.

2.2.1 Transition Probabilities

Time-dependent transition probabilities for the health states were derived from sub-group analysis of pooled tisagenlecleucel data using event-free survival, referred to as PFS in the model, and OS time-to-event data. The transition probability for PFS to RspPD was calculated as the difference in the proportion of patients in event-free survival (EFS) from one cycle to the next, multiplied by the RspPD probability from the KM curve at the respective time point, and is described using the following equation:

$$\text{RspPD} = \left[(S^{PFS}(t) - S^{PFS}(t+1)) \times S^{PD}(\text{t})\right] \times \text{P}_{\text{Rsp}}$$

where S^{PFS} is survival at time t from the EFS curve and S^{PD} is survival at time t derived from the OS curve for patients who had responded at 3 months then lost response or progressed. P_{Rsp} is the proportion of patients in response at the time of entering the STM. To adjust for the event of death in calculating the proportion of patients in the RspPD state, background mortality was applied using standardised mortality ratio (SMR)-adjusted time-varying probabilities from Australian life tables. Tunnel states were used to track patients moving from PFS to RspPD so that time-dependent transition probabilities could be assigned. In other words, transitions in the RspPD state were dependent on the time since the last transition, without there being a change in the actual health state [9]. The transition probability for NRspPD to death was estimated from OS data for non-responders at 3 months. The proportion of patients in the death state for the entire cohort was calculated as 1 minus the sum of all patients alive, as described by the following equation:

$$P_{Death}(t) = 1 - \left(P_{PFS}(t) + P_{RspPD}(t) + P_{NRspPD}(t)\right)$$

where P is the proportion of patients in each health state at time t.

For blinatumomab, time in PFS was estimated by reconstructing individual data from the published KM OS curve [22], adjusted by a constant cumulative HR of 0.83 between OS and PFS [17]. Time-to-event data for blinatumomab patients moving from PFS to PD was not available, therefore transition probabilities for tisagenlecleucel NRspPD were applied. For the blinatumomab arm of the model, tunnel states were also used to apply time-varying transition probabilities to patients moving from PFS to PD.

2.2.2 Long-Term Survival

Long-term transition probabilities were derived by fitting parametric models to survival data for each sub-group. Selection of parametric model was based on whether the model was statistically a good fit according to the Akaike information criterion (AIC) and Bayesian Information Criterion (BIC), and also whether the extrapolated portion was clinically and biologically plausible [31]. Extrapolations were applied from the point on the KM curve where patient numbers were small (< 12 patients) due to a high level of censoring [32]. Long-term survival beyond 5 years 'cure-point' was extrapolated using a general mortality probability derived from Australian life tables. General mortality was

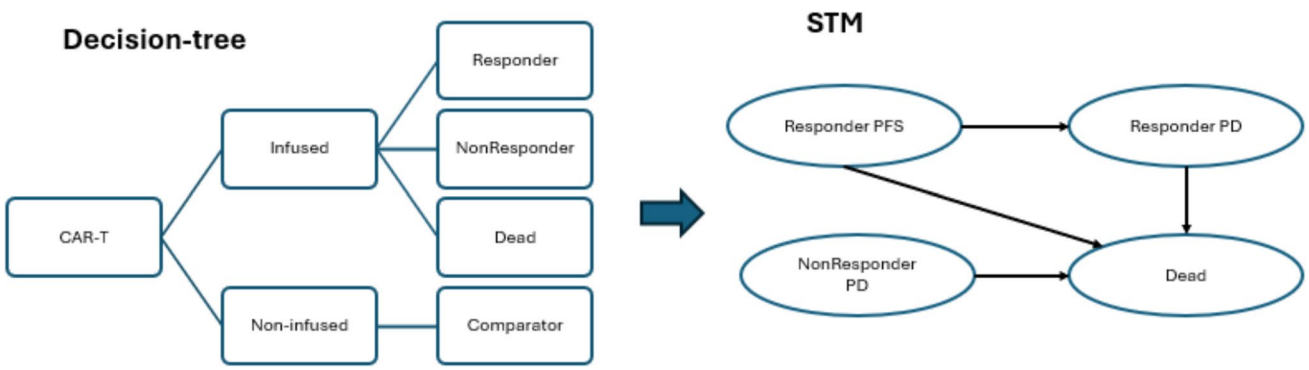

Fig. 1 State transition model structure with preceding decision tree for the CAR-T arm. *CAR-T* chimeric-antigen receptor T-cell therapy, *PD* progressive disease, *PFS* progression-free survival, *STM* state transition model

adjusted by applying a standardised mortality ratio (SMR) of 9.05 from a Canadian cohort study in childhood cancer patients who had survived at least 5 years [24] to the proportion of patients remaining in PFS. Although no gradual transition was incorporated when switching from the extrapolated curve to an SMR-adjusted general mortality, the impact of different 'cure-points' on the ICER was tested in sensitivity analyses.

2.3 Partitioned Survival Model Structure

The model was built in Microsoft Excel® using a monthly cycle length modelled over a lifetime horizon. Consistent with the approach for the STM, the tisagenlecleucel arm included an initial decision tree to accommodate an OBA, followed by a series of PSMs dependent on the patients' response status at 3 months. Unlike the STM, the proportion of patients who initially responded then progressed was estimated using AUC, calculated as the difference between the responder OS and PFS curves. Consistent with the STM approach, parametric models were used to extrapolate the observed data to year 5, after which SMR-adjusted all-cause mortality was applied. For the blinatumomab arm, a conventional three-health-state structure was applied with OS and PFS survival probabilities generated using the same approach as described for the STM.

2.4 Discrete Event Simulation Structure

Unlike the STM and PSM models, the DES model was developed using specialised software (Treeage Pro 2022, Williamstown, MA, USA) due to its computational complexity. The movement of patients through the model was determined by the probability of experiencing an event, randomly drawn from parametric time-to-event distributions [33, 34]. Unlike the STM and PSM approaches, the DES model explicitly included an infusion wait-time distribution for tisagenlecleucel, during which patients were at risk of manufacturing failure, a pre-infusion adverse event (AE) or death using probability distributions derived from different data sources. The model included a response assessment at 3 months to accommodate an OBA. The same data used for the STM was used to generate parametric probability distributions to calculate the time to event for patients in PFS and PD health states. Patients moved to a separate long-term health state at 5 years, where SMR-adjusted all-cause mortality was linked to individual patient age using bootstrapping. This meant that patients continued to remain in the health state in which they entered and were assigned the costs and QALYs from the relevant health, without moving to a progression state prior to death. For the blinatumomab arm, OS and PFS distributions were generated as described for the STM, although without access to individual patient data for blinatumomab, data for tisagenlecleucel non-responders were applied to patients in PD. Consistent with the approach for the tisagenlecleucel arm, patients alive at 5 years moved to a separate long-term health state where SMR-adjusted all-cause mortality was applied. In generating the base-case results, a total of 10,000 patient simulations were run. Additional simulations resulted in only minor changes to the results, by a matter of decimal places, with minimal impact on the ICER.

2.5 Utilities

The same utilities were applied to each model, with a pre-infusion utility applied to the DES model only. Utility values were calculated from patient-level EQ-5D-3L data from the ELIANA study using UK preference weights [35]. The PD state included EQ-5D assessments prior to infusion of tisagenlecleucel (while patients are in a progressive state) and after a PFS event, combined into a single PD utility. Utility data for patients prior to infusion with tisagenlecleucel was applied to the pre-infusion period in the DES. For blinatumomab, no published utility data were available, therefore 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 adverse events (SAEs) and subsequent SCT.

2.6 Costs

Cost inputs sourced from prior publications were adjusted for inflation using the Reserve Bank of Australia (RBA) inflation calculator [36], and when sourced from international publications, converted to Australian dollars (AUD) using RBA exchange rates [37]. All estimates of costs were calculated in AUD, although costs were reported in US dollars (USD), consistent with previous publications of the PSM and DES models [17, 38], using RBA exchange rates, April 2022 [37].The base case assumed a single payment of $375,000 for tisagenlecleucel at the point of infusion, converted from the NICE published price [25] as the Australian price is not publicly available. Costs associated with the administration of each treatment included the cost of leukapheresis, bridging chemotherapy (tisagenlecleucel only), cost of infusion, as well associated costs of managing serious AEs including tocilizumab for CRS and intravenous immunoglobulin (IVIg) for B-cell aplasia. The cost of SCT was included for the proportion of patients who received subsequent SCT in both the tisagenlecleucel and blinatumomab arms. The cost per course of blinatumomab was calculated using the Australian PBS price [26] as $49,127

(AUD 65,502) and an average number of treatment cycles from the clinical study [22], noting that the net price may be lower due to confidential pricing arrangements. In the DES model, treatment costs were applied as a one-off cost at the beginning of each decision node.

2.7 Model Assessment

A comparison of the models involved a quantitative assessment, in terms of costs, QALYs and the incremental cost-effectiveness ratio (ICER), and a checklist comprising the components captured by each model type, based on a set of parameters that affect the construction and outcomes of models for the cost effectiveness of CAR-T.

2.8 Quantitative Performance

Model traces were plotted to visualise the proportion of patients in PFS and PD over the first 5 years. Additionally, OS traces were graphed to assess any differences in the extrapolation of OS over a lifetime. Results were reported in LYs, QALYs and costs. Deterministic analysis was undertaken to test the impact of changes in CAR-T wait time, cure-point and duration of IVIg use as these parameters were considered uncertain due the lack of long-term data for CAR-T and in relation to CAR-T wait time, at risk of delay in clinical practice. The impact of removing the cure assumption completely so that extrapolation was independent of general mortality was also tested because previous studies identified greater differences in model results over the extrapolation period compared with the observed period [39, 40]. Additionally, sensitivity of the results to different OBAs was assessed by varying the rate of response at 3 months. Two different OBAs were tested, a split-payment arrangement (50% payment on infusion and 50% payment on response at 3 months) and a single payment on response only, using a weighted pricing approach so that the total cost for each OBA was equivalent to the base-case price of $375,000 for tisagenlecleucel, as described previously [17].

2.9 Checklist of Model Attributes

The components considered important in modelling the cost effectiveness of CAR-T were grouped into three categories pertaining to model flexibility, complexity and validity. Flexibility was defined as the ability to capture an OBA, incorporate CAR-T wait time and apply different long-term assumptions. Complexity was defined in terms of whether additional analysis of individual data was required, and validity in terms of the level of the concordance in the results generated.

3 Results

3.1 Quantitative Performance

3.1.1 Model Traces

A comparison of the model cohorts by health state showed similar proportions of patients in PFS, PD and dead over the first 5 years, with minor variations by timepoint (Fig. 2). The apparent smoothness of the DES curves is due to the use of probability distributions to model the movement of patients through the health states, compared with STM and PSM approaches that rely on the observed data over the within-trial period. The consistency in the models over the longer-term extrapolation period is demonstrated by a comparison of OS curves which are aligned from the point of extrapolation of the observed data for tisagenlecleucel and blinatumomab (Fig. S1, see ESM).

3.1.2 Base-Case Results

Base-case results by model type were relatively similar (Table 2; Fig. 3). All models generated similar incremental QALYs and costs, resulting in ICERs ranging from $96,074 per QALY for the DES model to $99,625 per QALY for the STM.

3.1.3 Sensitivity Results

Changes in the cure-point assumption, duration of IVIg use and CAR-T wait time yielded the greatest impact on the ICER with results reasonably consistent by model type, albeit DES was the only model to capture the impact of a change in CAR-T wait time (Fig. 4; Table S2 in the ESM). The impact of different payment arrangements under varying response rates was also consistent across each model type, with a single payment on infusion (applied in the base case) resulting in the greatest variation in the ICER, and a responder-only payment arrangement resulting in minimal change to the ICER when tested by varying the rate of response to CAR-T at 3 months. Adjusting the long-term extrapolation approach in the STM and DES models so that the cure assumption was applied to patients in PFS only had a minor impact on the ICER results.

3.2 Checklist of Model Attributes

In terms of model flexibility, all models incorporated an OBA, although only the DES model included the ability to test the impact of change in CAR-T wait time on cost effectiveness. There was flexibility to apply different long-term assumptions by health state in the DES model

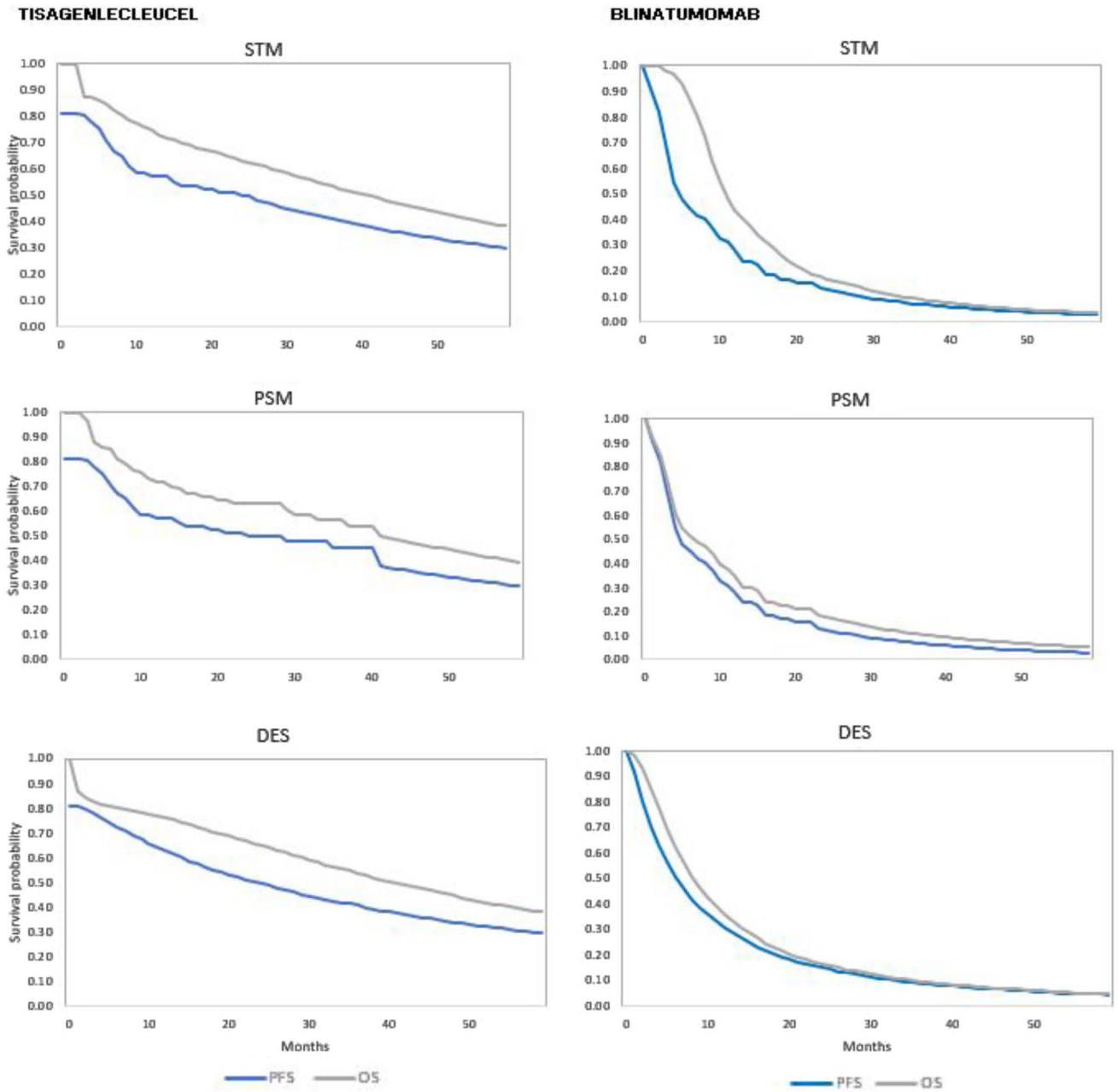

Fig. 2 Health state occupancy for each model structure for tisagenlecleucel and blinatumomab. *DES* discrete event simulation, *OS* overall survival, *PFS* progression-free survival, *PSM* partitioned survival model, *STM* state transition model

and STM, but not the PSM. All models were considered complex because analysis of individual data from the clinical trials was required to populate each model. All models were considered valid based on the similarity of the results in the quantitative comparison (Table 3).

4 Discussion

Our base-case analyses showed reasonable consistency in results across the STM, PSM and DES models in terms of benefit and costs for tisagenlecleucel and blinatumomab. The consistency in results was demonstrated in the similarity in the proportion of patients residing in each of the health states—PFS, PD and dead—over the first 5 years, supported by the alignment of the OS curves beyond the observed data period. Minor variations were observed,

Table 2 Base-case results

	STM	PSM	DES
LYs discounted			
Tisagenlecleucel	6.96	7.12	7.43
Blinatumomab	1.75	1.80	1.75
Incremental	5.21	5.32	5.68
QALYs discounted			
Tisagenlecleucel	5.32	5.43	5.79
Blinatumomab	1.16	1.19	1.19
Incremental	4.16	4.24	4.60
Costs discounted			
Tisagenlecleucel	$602,734	$610,018	$622,872
Blinatumomab	$188,008	$189,911	$181,219
Incremental	$414,726	$420,107	$441,652
Cost per LY	$79,578	$78,978	$77,729
Cost per QALY	$99,625	$99,038	$96,074

Costs in US dollars

DES discrete event simulation, *LY* life-year, *PSM* partitioned survival model, *QALY* quality-adjusted life-year, *STM* state-transition model

particularly during the within-trial period, which were expected due to the different modelling approaches, in particular the application of different sub-group analyses of the tisagenlecleucel data to estimate OS of the entire cohort. The DES model generated the most LYs and QALYs for tisagenlecleucel, with an additional 0.47 incremental LYs and 0.43 incremental QALYs compared with the STM, which generated the least QALYs. The small, additional outcomes benefit generated by the DES was offset by the additional costs associated with ongoing disease management due to an improvement in survival; consequently, the cost per QALY for each model was similar. Of note, there was potential confounding due to the different model types, although this was considered negligible due to the similarity in the model traces showing a similar proportion of patients in each health state over time.

In sensitivity analysis, cost effectiveness was most impacted by changes to the cure-point assumption, duration of IVIg use and CAR-T wait time with the percentage change in the ICER relative to base case consistent by model type, albeit DES was the only structure that allowed for CAR-T wait time to be tested, substantially reducing the benefit of CAR-T when wait time was extended. Models also generated similar results when the impact of different OBAs were tested by varying response rates, validating the results of a previous study designed to assess the impact of different OBAs on alleviating cost effectiveness uncertainty of CAR-T in young ALL patients [17]. This analysis supports the original findings that OBAs have a modest impact on alleviating cost-effectiveness uncertainty relative to other parameters in modelling the cost effectiveness of CAR-T.

To our knowledge, this is the first study to compare the results generated from different model types for a CAR-T therapy. Previous studies have evaluated PSM versus STM approaches and STM versus DES approaches, although no studies that compared all three modelling approaches were identified. Previous studies comparing PSM and STM approaches have generated different results. A study by Cranmer et al. [40] applied PSM and STM approaches using data in late-stage cancer patients. The PSM produced ICERs between £234,829 and £522,963, whereas the STM generated ICERs ranging from dominant to over £7 million. The authors reported that this large variation in results was driven by differences in outcomes beyond the observed period. Smare et al. [39] evaluated the impact of PSM and STM approaches on survival estimates of different therapies

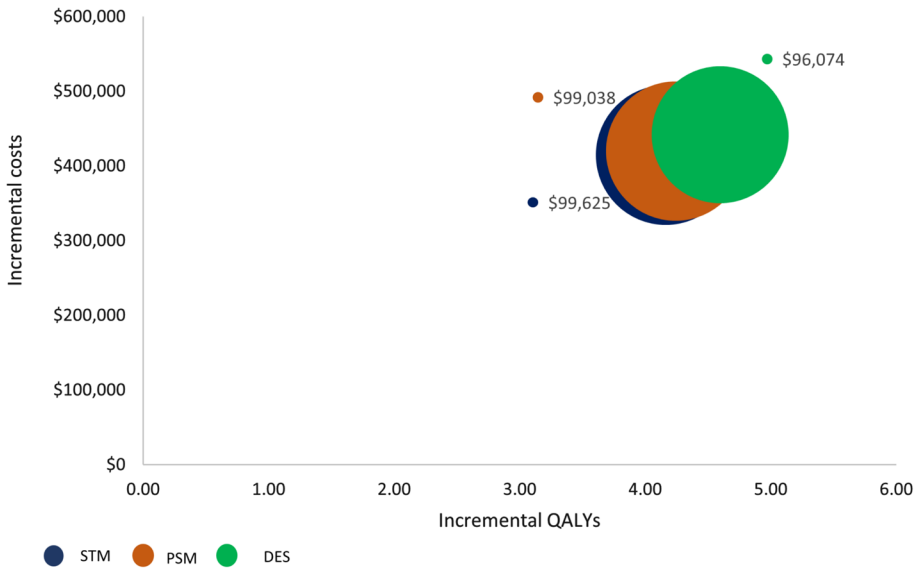

Fig. 3 Bubble plot of base-case results by model type. Note: Circle size is proportional to the ICER. *DES* discrete event simulation, *ICER* incremental cost-effectiveness ratio, *PSM* partitioned survival model, *STM* state transition model, *QALY* quality-adjusted life-year

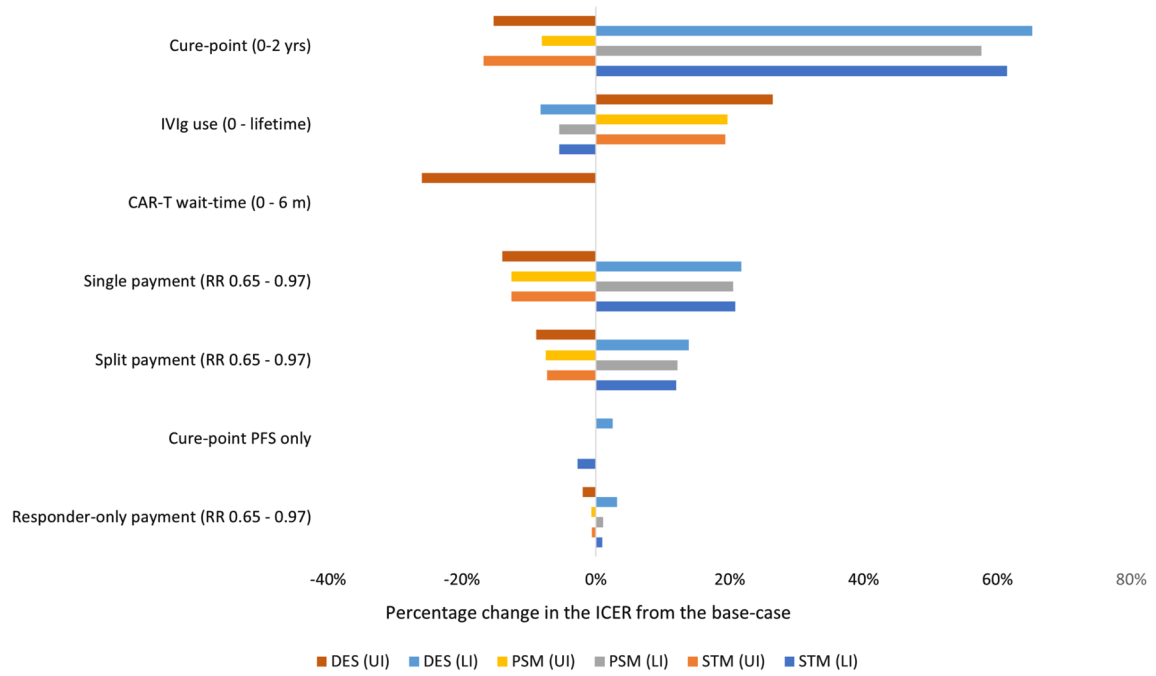

Fig. 4 Tornado diagram of the results of the sensitivity analyses, showing the percentage change in the ICER from the base-case by model type. Note: *Blue bars* indicate the lowest parameter from the base case (*LI*, lower interval) and *red bars* indicate the highest parameter value from the base case (*UI*, upper interval). *CAR-T* chimeric-antigen receptor T-cell therapy, *DES* discrete event simulation, *PSM* partitioned survival model, *RR* response rate, *STM* state transition model

Table 3 A checklist to consider when selecting the type of model to assess the cost effectiveness of CAR-T

Category	Attribute	STM	PSM	DES
Flexibility	The impact of change in CAR-T wait time on cost effectiveness could easily be tested	X	X	✓
	An OBA could be incorporated by linking response to long-term outcomes and costs	✓	✓	✓
	There was flexibility to apply different long-term assumptions by health state	✓	X	✓
Complexity	The model could be populated using the published data, without the requirement for additional analysis using individual patient data	X	X	X
Validity	The model generates similar results to alternative model types of the same therapy and patient population	✓	✓	✓

✓ indicates 'yes', X indicates 'no'

CAR-T chimeric antigen-receptor T-cell therapy, *DES* discrete event simulation, *OBA* outcomes-based payment arrangement, *PSM* partitioned survival model, *STM* state transition model

in renal cell carcinoma, reporting consistent results for the within-trial period, although differences became apparent when data were extrapolated over a 20-year time horizon [39]. We did not observe such extreme variations between STM and PSM in our study, suggesting that post-progression survival data for tisagenlecleucel derived from a sub-group analysis of progressed patients were reliable for modelling OS.

Results from studies comparing STM and DES models, however, have generated more consistent results. In a cost-effectiveness analysis of treatment in metastatic colorectal cancer, STM and DES models generated similar time-to-event curves and similar cost-effectiveness outcomes, although the DES more accurately reflected the mean health state duration of the trial [33]. Similarly, Senanayake et al. [41] found that predictions from the DES model were a better match for the actual data than the STM in modelling cost effectiveness of kidney transplant quality. A systematic review by Standfield et al. [42] compared STM and DES models applied to cost-effectiveness analyses of healthcare technologies, concluding that the major advantage of DES was the ability to incorporate individual patient history and resource constraints, where this is a driver of cost effectiveness, although the disadvantages of DES were the level of complexity due to the additional detail required in modelling

complex systems, and skill needed to develop the model [42].

We developed a checklist to summarise the criteria captured by each model type considered important in modelling the cost effectiveness of CAR-T. Each model was developed to incorporate an OBA, by linking response to long-term outcomes and costs. In our experience of building each model, it was easier to incorporate an OBA using DES due to the ease in which it can incorporate more complex treatment pathways by calculating the time to a competing event, without the need for separate health states. However, we acknowledge that the capacity to incorporate complex events may depend on the type of modelling software used, as opposed to the model structure per se.

DES was the only model to explicitly model infusion wait time using external OS data to model outcomes for patients when wait time was increased/decreased. During the wait-time period, patients could experience an adverse event, manufacturing fail, proceed to infusion or die. Although the STM and PSM didn´t include a specific wait-time state, the underlying data and transition probabilities captured a static wait-time effect. While changes in wait time could be incorporated using PSM and STM, this would require the use of tunnel states to model the transition of patients into different health states during the pre-infusion phase. The role of resource constraints and wait times is growing in importance when evaluating cell therapies, especially as these treatments move to earlier points within care pathways with larger patient populations [43, 44]. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidance on modelling good research practices recommends, where access to treatment may be subject to limited resources, the impact of resource constraints should be captured [11], reinforcing the importance of incorporating wait time.

All models required analysis of individual data to incorporate the OBAs, to link response outcomes to survival for CAR-T patients. STM and DES models required further analysis of individual data to estimate OS for patients in post-progressive disease, which was not needed for the PSM owing to its AUC methodology to derive the proportion of patients in PD. All models were considered to meet the validity criterion, given the concordance of the results generated.

While the additional complexity required to build and populate a DES model is a disadvantage over other approaches, this may be justified where additional complexity is needed to ensure key drivers of cost effectiveness are addressed [11, 42]. Additionally, due to the continuous measure of time, without the limitation of fixed time intervals, DES may lead to more accurate estimates of the timing of outcomes [45]. We were able to link individual patient age to all-cause mortality in the DES, potentially giving more accurate estimates of long-term survival outcomes than the mean, as patient characteristics are rarely normally distributed [46]. This is especially relevant when applying all-cause mortality over a lifetime in patients as young as 3 years. Others have similarly suggested DES as a preferable method over other model types due to its ability to better represent clinical practice and approximate the actual data [33, 46].

Further work is needed to validate the set of criteria to discern the appropriate model structure for CAR-T. This could involve an elicitation process with stakeholders, with consideration given to weighting each of the attributes according to their impact on evaluators and decision makers. In our experience, DES was more amenable to modelling complex pathways, namely CAR-T wait time, albeit we did not attempt to model changes in CAR-T wait time using PSM and STM, and this could be influenced by the modelling software used. Further work could explore incorporating tunnel states into PSM and STM models at the pre-infusion phase. Our findings for CAR-T do not necessarily transfer to other decision problems and technologies beyond CAR-T.

4.1 Limitations

Models were compared on the sensitivity of certain parameters using deterministic analysis. Probabilistic sensitivity analysis (PSA) was not considered in building each of the models (of which the PSM and DES have been published previously [17, 38]) due to the Australian setting in which these models were based. HTA authorities in Australia require the presentation of deterministic analyses only. A key limitation of the DES model is its long run time when conducting probabilistic analysis due to DES being probabilistic in its approach; therefore, subjecting individual patient simulations to subsequent probabilistic analysis is computationally burdensome and arguably unnecessary given that it is inherent in the model [47]. While PSA can inform HTA decision making by assessing the level of uncertainty surrounding the ICER, the purpose of this analysis was to compare results across different model types. We note that our approach is consistent with that of a previous study by Cranmer and colleagues that did not incorporate PSA when comparing results of PSM and STM approaches [40].

5 Conclusion

CAR-T therapy is characterised by early-phase data, high upfront costs, as well as a complex manufacturing and administration process compared with conventional therapies. DES is a modelling approach which may provide

greater flexibility to deal with these elements compared with STM and PSM approaches, in terms of capturing more complex components such as OBAs and wait time. Ultimately, determining the most appropriate model structure will require longer-term data to assess the true predictive value of each model.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-024-01430-7.

Declarations

Conflict of interest Amy Gye is an employee of Novartis Pharmaceuticals. Stephen Goodall and Richard De Abreu Lourenco have no conflicts to disclose.

Author contributions Concept and design: Gye, Goodall, De Abreu Lourenco; acquisition of data: Gye; analysis and interpretation of data: Gye; drafting of the manuscript: Gye, Goodall, De Abreu Lourenco; critical revision of the paper for important intellectual content: Goodall, De Abreu Lourenco; supervision: Goodall, De Abreu Lourenco.

Data availability statement Individual data used to support this study are not publicly available for ethical and legal reasons. All other sources used in this research are referenced and publicly available.

Funding This research is part of an Industry Doctorate Program at the Centre for Health Economics Research and Evaluation, University of Technology Sydney in collaboration with Novartis Pharmaceuticals Australia. Novartis Pharmaceuticals Australia provided a Research Support Fee.

Role of the Funder/Sponsor The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation of the manuscript. The manuscript was reviewed by Novartis prior to submitting for publication. The views expressed are those of the authors and not necessarily those of Novartis Pharmaceuticals or the Centre for Health Economics Research and Evaluation (CHERE).

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