UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Is there a need for a different methodological approach to modelling the cost-effectiveness of cell and gene therapies?

by Amy Gye

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

under the supervision of Professor Stephen Goodall and Professor Richard De Abreu Lourenco

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Certificate of Original Authorship

I, Amy Gye declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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And last but not least, my partner in life, who was supportive while we navigated our way through the COVID pandemic, survived homeschooling two small children (just) while trying to find the time to work in our respective jobs. Those were interesting times.

Thesis format

This thesis is structured as a compilation of chapters and published/submitted manuscripts. The thesis begins with an introductory chapter to provide an overview of the research area and aims, followed by four original research chapters, each addressing one of four separate key objectives. The thesis ends with a final discussion chapter discussing the main conclusions, limitations, and areas for further work. Where necessary, some typographical edits and other minor edits after review by the examiners, have been made to the original publications. Where acronyms are introduced, they are applied throughout the whole thesis, and not reintroduced in each chapter.

Manuscripts

Gye A, De Abreu Lourenco R, Goodall S. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared With Older Patients. *Value in Health*. 2021;25(1):47-58. doi:10.1016/j.jval.2021.07.008

Gye A, Goodall S, De Abreu Lourenco R. Cost-effectiveness Analysis of Tisagenlecleucel Versus Blinatumomab in Children and Young Adults with Acute Lymphoblastic Leukemia: Partitioned Survival Model to Assess the Impact of an Outcome-Based Payment Arrangement. *Pharmacoeconomics*. 2023 Feb;41(2):175-186. doi:10.1007/s40273-022-01188-w

Gye A, Goodall S, De Abreu Lourenco R,. (in press) Discrete Event Simulation to Incorporate Infusion Wait-Time when Assessing Cost-effectiveness of a Chimeric-antigen Receptor T-cell Therapy. *Value in Health.*

Gye A, Goodall S, De Abreu Lourenco R,. (In Press) Different Models, Same Results: Considerations When Choosing Between Approaches to Model Cost-effectiveness of Chimeric-antigen Receptor T-cell Therapy. Pharmacoeconomics.

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Abbreviations list

ABMTRR	Australian Bone Marrow Transplant Recipient Registry
AE	Adverse event
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
AUC	Area under the curve
AUD	Australian dollars
BIC	Bayesian information criterion
CADTH	Canadian Agency for Drugs and Technology in Health
CARs	Chimeric antigen-receptors
CAR-T	Chimeric antigen-receptor T-cell therapy
CED	Coverage with evidence development
CI	Confidence interval
CIBMTR	Centre for International Blood and Marrow Transplant Research
CR	Complete remission
CRi	CR with incomplete blood count
CRS	Cytokine release syndrome
DES	Discrete event simulation
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EFS	Event-free survival
EQ-5D	EuroQoL-5 Dimension
EQ-5D-3L	EQ-5D-3 Levels
HCT	Hematopoietic cell transplantation
HR	Hazard ratio
HST	Highly specialised technologies
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVIg	Intravenous immunoglobulin
IPD	Individual patient data
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LY	Life year
MAP	Managed access program

MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHRA	National Health Reform Agreement
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
OBA	Outcomes-based payment arrangement
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PD	Progressive disease
PFS	Progression-free survival
PSM	Partitioned survival model
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RBA	Reserve Bank of Australia
RWD	Real world data
RWE	Real world evidence
RCT	Randomised controlled trial
r/r	Relapsed or refractory
SAE	Serious AE
SCT	(allogenic) Stem cell transplant
SMA	Spinal muscular atrophy
SMC	Scottish Medicines Agency
SMR	Standardised mortality ratio
STM	State-transition model
TGA	Therapeutic Goods Administration
TLV	Swedish Dental and Pharmaceutical Agency
USD	US dollars
WHO	World Health Organization
ZiN	National Health Care Institute, Netherlands

Abstract

Chimeric antigen receptor T-cell therapies (CAR-Ts) were the first cell and gene therapies registered globally and considered for public funding via a health technology assessment (HTA) process. Access to CAR-T provides a potential cure for patients with certain blood cancers where previously there were limited alternatives and survival outcomes were poor. At the same time, these novel therapies have disrupted health care systems and challenged public funding decisions. While many of the issues in assessing the value of CAR-Ts are similar other medicines, particularly in oncology, complex manufacturing, potential for cure and high up-front costs make CAR-T unique. These elements combined have made assessing their cost-effectiveness for HTA purposes particularly challenging.

Using the CAR-T, tisagenlecleucel, for the treatment of young patients with relapsed or refractory (r/r) acute lymphoblastic leukaemia (ALL) as a case-study, the research objectives were: (1) identify sources of uncertainty in modelled economic evaluations of CAR-Ts considered by HTA agencies, (2) assess the utility of outcome-based payment arrangements (OBAs) as a mechanism for managing long-term clinical and economic uncertainty using a de novo modelling approach, (3) explicitly model the CAR-T treatment pathway to capture the impact of CAR-T infusion wait-time using discrete event simulation (DES), and (4) compare different modelling techniques to assess the impact of structural uncertainty on cost-effectiveness.

In addressing each of these objectives, this research demonstrates the importance of designing flexible model structures to incorporate OBAs to determine a suitable payment structure, outcome selection, and contractual conditions for implementation. The importance of considering the process of CAR-T in model design is evident, as delay in infusion of CAR-T resulted in substantial reduction in benefit at a population level. Overall, this research highlights the need for a bespoke modelling approach for CAR-T to identify the main sources of uncertainty impacting cost-effectiveness to aid decision-making at the initial point of assessment and facilitate speed of access to patients.

Chapter 1: Introduction

Overview

Cell and gene therapies are potentially one-time curative therapies, often for the treatment of life-threatening diseases in young patients and have been associated with very high upfront costs[1]. To-date, cell and gene therapies have received marketing authorisation for the treatment of life-threatening diseases including blood cancers and genetic diseases, following progression after multiple prior therapies[2, 3]. Cell and gene therapies work to repair or enhance cells at the genetic level with the potential to alleviate the underlying cause of genetic and acquired diseases[4]. Cell therapies are distinct from gene therapies, and a therapy can be both a cell and a gene therapy combined. Cell therapies are modified outside the body before being injected into the patient (*ex vivo*), and cells may originate from the patient (autologous cells) or a donor (allogeneic cells)[5]. Currently available gene therapies use vectors to alter genes in certain types of cells which can occur in vivo or ex vivo [6,1]. CAR-Ts are both a cell and a gene therapy because cells are genetically modified outside of the body before being infused into the patient[2]. The CAR-Ts, tisagenlecleucel and axicabtagene ciloleucel for the treatment of paediatric ALL and diffuse large B-cell lymphoma (DLBCL) were among the first cell and gene therapies to be registered globally, followed by the gene therapies, onasemnogene abeparvovec for spinal muscular atrophy (SMA) and voretigene neparvovec for vision loss[7, 8].

To date, registration of cell and gene therapies has been based on early phase, single arm clinical trials, where it has been unfeasible to conduct a randomised controlled trial (RCT) due to small patient numbers and the ethical dilemma of allocating patients to a control arm where, in the absence of an effective treatment, the disease leads to premature mortality [9]. Faster regulatory approval timelines have been applied to cell and gene therapies via priority pathways where regulators consider the potential benefit demonstrated in early phase trials support expedited

[1]In vivo therapy is administered directly into the body, whereas ex-vivo therapy occurs outside the body in cells isolated from the patient.

approval, outweighing the risk of waiting for additional data from phase III studies[10]. However, countries that utilise HTA to inform reimbursement decisions of new medical technologies face even greater challenges when it comes to assessing the value of cell and gene therapies, given the evidence is limited and the upfront costs per patient are very high. Establishing value for money, i.e., using economic evaluation to determine the cost-effective price for a potentially curative, one-time treatment, is associated with a high level of uncertainty, especially where the lifetime incremental benefit is derived from single-arm studies and immature data. Use of surrogate endpoints, lack of comparative evidence, small sample sizes and the need for long-term extrapolation of survival endpoints are some of the major hurdles identified by HTA agencies in assessing the value associated with existing cell and gene therapies[11]

Tisagenlecleucel was one of the first cell and gene therapies registered in countries including the US, EU and Australia, and consequently among the first to be considered for public funding via an HTA process[12-14]. Therefore, tisagenlecleucel was selected for this research as it provides a test-case to investigate how current HTA processes are applied to these novel technologies. The population selected for study was young patients with ALL because an initial review of HTA evaluations indicated that assessing the cost-effectiveness in young patients was associated with the greatest uncertainty in terms of the magnitude of long-term benefit compared with older patients[15]. Novartis Pharmaceuticals is the manufacturer of this technology and individual patient data from the clinical trials were accessible as part of this Doctorate. While this research focuses on the HTA process in Australia, findings are likely applicable to HTA processes globally.

Importance of the research

It is estimated that there will be around 40 to 50 cell and gene therapies marketed by 2030, with 12 in the next 5 years, with half of all products marketed by 2030 expected to be in B-cell lymphomas and leukaemia[16]. As of January 2021, there were 130 clinical trials ongoing in Australia in cell and gene therapies[17]. With an increasing number of cell and gene therapies expected to progress to registration at a faster pace than conventional therapies, HTA agencies and governments are

under increasing pressure to make potentially high financial risk decisions due to the high, upfront cost associated with cell and gene therapies, supported by limited evidence. Equally, there is pressure on manufacturers to enter into agreements with government that place them at increased financial risk where a therapy may not perform as well as expected, and risk-share arrangements may require remuneration contingent on OBAs or require a refund where pre-determined conditions are not met[18]. Investigating alternative approaches of assessing cost-effectiveness and financial impact uncertainty associated with cell and gene therapies is therefore the focus of this research.

Background

CAR-T therapy

Tisagenlecleucel is indicated for the treatment of children and young adults r/r ALL and adults with r/r DLBCL [19]. The manufacturing process for CAR-T cells is relatively complex compared with conventional therapies (Figure 1), involving a number of steps starting with the collection of white blood cells from the patient through the process of leukapheresis and T-cell extraction[20]. The T-cells are frozen and transported to a manufacturing facility where they undergo genetic modification and expansion. T-cell receptors are genetically modified via a viral vector to bind to specific antigens present on cancer cells, known as chimeric antigen receptors (CARs)[21]. Tisagenlecleucel is genetically modified to target CD19 receptors on the surface of B-cells present in B-cell malignancies including non-Hodgkin lymphoma and leukaemia[22]. The engineered CAR-T cells are then infused back into the patient over a single infusion of approximately 30 minutes, usually after the patient has undergone lymphodepleting chemotherapy to decrease immunosuppressive cells which may improve effectiveness of the modified T-cells[20]. Due to the potential for acute adverse reactions, particularly the development of cytokine release syndrome (CRS), administration often occurs in the inpatient setting where patients have access to emergency care[20]. Due to the process involved in manufacturing CAR-T cells, there is a wait-time period, from the time of leukapheresis to infusion of the modified cells. In the pivot trial of tisagenlecleucel in children and

young adults with ALL, the median 'wait-time' for CAR-T cells was 1.5 months (range, 1.0 – 3.5 months)[23]. In clinical practice, this may be subject to considerable variation depending on where the manufacturing site is located and capacity constraints.

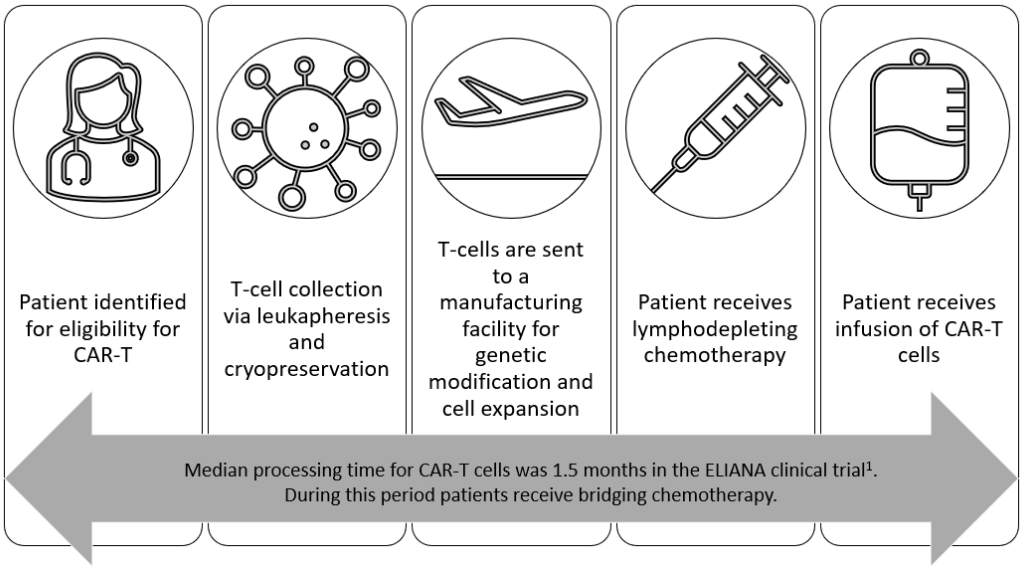


Figure 1 CAR-T manufacturing process

Adapted from Nair and Weston[20]; Kaufman et al.[3]
[1]Maude et al. [23]

Health Technology Assessment

HTA is a means of ensuring rational and efficient use of health care resources based on a systematic approach to evidence selection, aimed at improving access to medicines[24]. The World Health Organization (WHO) provides guidance on the methods and processes for HTA[25], although how HTA is implemented including whether there is a legislative requirement to consider HTA in making decisions to fund health technologies differs by country. Countries with established HTA systems have their own set of guidelines and processes for decision-making, such as the National Institute for Health and Care Excellence (NICE) in the UK[26], the Canadian Agency for Drugs and Technologies in Health (CADTH)[27], and the Pharmaceutical Benefits Advisory Committee (PBAC)[28] and Medical Services Advisory Committee (MSAC)[29] in Australia. In Australia, the PBAC has a legislative requirement under the National Health Act to consider the comparative effectiveness and cost of medicines proposed for Government funding[28], and a positive recommendation from the

PBAC is required before a medicine can be subsidised via the Pharmaceutical Benefits Scheme (PBS)[28, 29]. MSAC is a non-statutory committee and provides advice to Government on whether a new medical service should be publicly funded on the Medicare Benefits Schedule (MBS)[30]. MSAC also advise Government on public funding decisions for high cost, highly specialised therapies for delivery in a public hospital setting under the National Health Reform Agreement (NHRA)[31].

The same HTA process that is used for conventional therapies is applied to cell and gene therapies. Tisagenlecleucel was assessed by MSAC for public funding because it was classified as a Class 4 Biological, comprising live animal cells or live animal tissue[32], by the Australian regulator, the Therapeutic Goods Administration (TGA)[33], and therefore was not eligible for consideration by PBAC, whose remit is pharmaceuticals[28]. Additionally, tisagenlecleucel was considered a high cost, highly specialised therapy for delivery in a public hospital setting under the NHRA.

PBAC and MSAC provide guidance to industry, and other non-industry sponsors on the approach to assessing comparative health gain and comparative cost-effectiveness, with a strong preference for evidence from RCTs to reliably inform decision-making[29, 34]. The PBAC guidelines specify other factors that are influential in decision-making including equity, therapeutic alternatives, severity of the medical condition, and whether the therapy can be targeted to patients who have the greatest potential to benefit, although the degree of influence these factors have on decision-making is unquantified. The MSAC guidelines also refer to similar qualitative factors [29]. Economic evaluation provides a quantitative measure as an input for decision-making, and the PBAC and MSAC guidelines state a preference for cost-utility analysis expressed in terms of quality-adjusted life years (QALYs) where there is superior or, less commonly, inferior therapeutic benefit to provide an overall measure of incremental cost-effectiveness via the incremental cost-effectiveness ratio (ICER)[29, 34].

Clinical and economic uncertainty are long-standing issues with which HTA agencies have grappled[35]. One of the major sources of uncertainty in economic evaluation is the level of available evidence, with the highest level of evidence being RCTs[36]. Single-arm trials can pose the biggest

source of uncertainty, as any measure of incremental benefit needs to be derived from a comparison to a historical control and this can be associated with a number of confounders, leading to uncertainty around the effect size[1, 37]. Applicability issues may arise if the clinical trial population is not directly representative of the intended population in practice, or the outcome measures in the trial do not represent long-term clinical outcomes[38]. For cell and gene therapies, it is widely proposed that ongoing collection of data is key to addressing the gaps in clinical trial evidence, via patient registries and long-term follow-up of clinical trial data via managed access programs (MAPs). This allow for additional, more mature data to be re-evaluated at a later time point to assess whether the initial estimates used to inform cost-effectiveness were aligned with actual data[1, 37, 39, 40].

Managed Access Programs

MAPs are a mechanism used by funding agencies to manage issues associated with limited clinical trial data and provide access to treatments that would otherwise not be recommended for public funding due to the uncertainty in cost-effectiveness. In the UK, oncology medicines and more recently cell and gene therapies have been given conditional recommendations by NICE while additional data is collected before a final assessment is made for funding under the National Health Scheme (NHS)[41-44]. In Australia, MAPs facilitate earlier funded access to therapies where there is high unmet clinical need but unacceptably high clinical and economic uncertainty. There is a formalised framework for MAPs under the PBS[45], although no established arrangement exists for MBS or NHRA funded technologies[30]. Several oncology medicines, including crizotinib, trametinib and pembrolizumab, have been listed on the PBS under the conditions of a MAP as a way of providing earlier PBS access while longer-term, more robust evidence, is generated[46].

MAPs can be categorised into two main types: non-outcome-based schemes and outcome-based schemes[39] (Figure 2). Non-outcome-based schemes include price-volume agreements, upfront discounts, and financial caps, whereas outcome-based schemes link price to an observed clinical outcome and can be at the individual or population level. At the individual level, payment for a

treatment can vary depending on the outcome observed in each patient[47]. At a population level, funding may be modified following a period of data collection and analysis, referred to in some countries as coverage with evidence development (CED)[39, 46]. The terminology referring to outcome-based schemes is varied, and includes performance- based risk share arrangements, pay for performance schemes, and performance-based agreements (among other terms). For the purposes of this research, the term OBA is used to define an agreement between the government and manufacturer that links the price of a product to a clinically relevant outcome at the individual patient level.

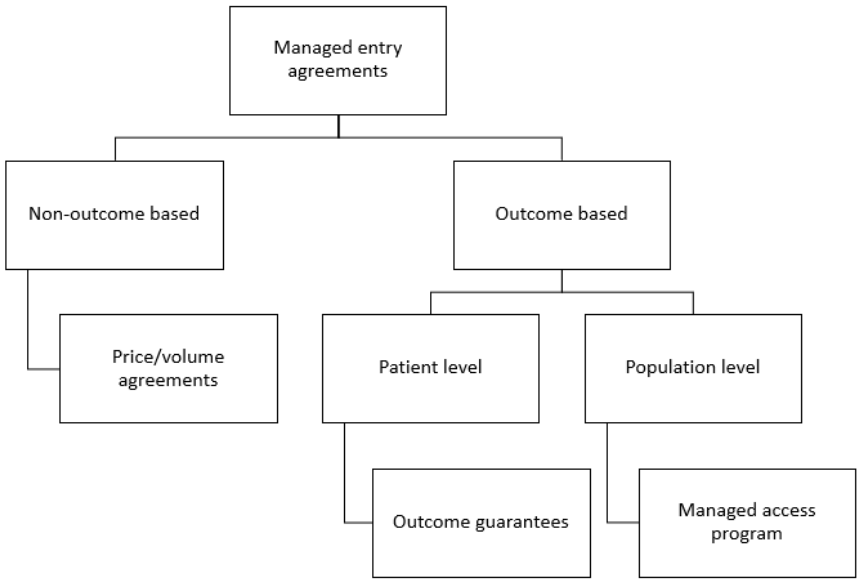


Figure 2 Taxonomy of Managed Access Programs

Adapted from Vitry and Roughhead[39]

Although MAPs offer a method of providing early access to novel treatments, whilst sharing the risk between the manufacturer and government, the scheme has been considered under-utilised in Australia[48] perhaps due to the experience with prior MAPs, albeit limited. In the case of crizotinib, 12-month survival data collected from patients treated on the PBS was consistent with the estimated survival based on the trial evidence originally presented in the PBAC submission, hence crizotinib continued to be funded on the PBS at the initial cost-effective price[46, 49]. For

pembrolizumab, the results from an updated model including an additional 2-years of survival data were not considered to meet the conditions specified in the MAP, and PBAC did not recommend a price increase as requested by the sponsor, although pembrolizumab continued to be listed on the PBS at the initial price[46, 50]. For trametinib, the estimated survival benefit was not supported by the updated analysis, therefore the sponsor was required to rebate to the Government the difference between the initial price and the lower price generated when the reduced survival benefit was applied in the economic model[46, 51].

Although there is no formalised arrangement for MAPs as part of the MSAC process, recent recommendations pertaining to CAR-T therapies have been contingent on the requirement of a review of cost-effectiveness and other matters including cost to Government. MSAC recommendations for the CAR-Ts tisagenlecleucel and axicabtagene ciloleucel were conditional on a review of clinical effectiveness, cost-effectiveness, and budget impact 2 years after the commencement of public funding. This arrangement also required data on the use of CAR-Ts, including data on patient outcomes, adverse events, and the use of high cost medicines, to be collected by the Australian Bone Marrow Recipient Registry (ABMTRR), with the cost of data collection incurred by the sponsors. Additionally, payment to the sponsors for the product was contingent on the patient receiving a successful infusion which meets the TGA specified minimum number of CAR-T cells[14, 52].

OBAs have been gaining traction as a potential way of addressing clinical uncertainties and financial risk associated with cell and gene therapies, from the perspective of the payor, to avoid high upfront payments and mitigate the impact of situations where expected benefits may not be realised in practice [37, 40, 53-57]. Other advantages of OBAs include incentivising evidence generation where payment is contingent on a pre-defined clinical outcome, requiring collection of real world data using registries, as well as better use of medicines in patients who are likely to benefit most and facilitating early patient access[47]. Additionally, OBAs result in the collection of real world evidence which may be beneficial to demonstrate the long-term clinical effectiveness of therapies[40],

particularly for rare indications that are more likely to be associated with limited clinical data[58]. Real world evidence may also be more pragmatic than evidence from a clinical trial setting, since data are from the population that use the technology, rather than a selected subset of the trial population. While there has been much discussion in the literature of the application of OBAs to cell and gene therapies, there is limited information on whether the use of OBAs, particularly in the context of HTA, leads to better value for money[59].

Payment for a one-time, potentially curative cell and gene therapy requires consideration of different payment structures and approaches because costs are upfront and cannot easily be recovered if the patient does not benefit, as opposed to conventional therapies where treatment, and subsequent payments thereof, can be more readily stopped once the patient stops benefitting[60]. There are several different ways of structuring payments for cell and gene therapies:

1. Conventional upfront payment for all patients, with no recovery of costs when expected benefits are not realised in practice (risk weighted towards government).
2. Partial upfront payment followed by payment on a clinical outcome being achieved (shared risk).
3. Delayed payment entirely contingent on an outcome being achieved (risk weighted towards the manufacturer or sponsor of the product).

Determining the most appropriate structure for an OBA can be difficult as consideration needs to be given to how real-world outcomes will be monitored and the data collected, as well as how the price for an outcome is determined [61]. Furthermore, consideration needs to be given to how OBAs might be incorporated into an assessment of cost-effectiveness, and what additional value OBAs can add, in terms of alleviating cost-effectiveness uncertainty, to a value-based price determined at the point of conducting an HTA.

Modelling cost-effectiveness

Determining the price for an OBA requires an economic model. There are several different methodological approaches that may be used to model the relative costs and benefits of a therapy to assess its cost-effectiveness as the basis for determining the value-based price within an OBA. Partitioned survival models (PSMs), state-transition models (STMs) and discrete-event simulation (DES) are the most frequently applied techniques for assessing the cost-effectiveness of healthcare interventions to-date[62, 63]. The application of mixture-cure models in oncology is also discussed.

Partitioned survival models

PSMs are the most common economic modelling approaches used in oncology and have been frequently applied in modelling the cost-effectiveness of cell and gene therapies due to the reporting of time-to-event outcomes, overall survival (OS) and progression-free survival (PFS). PSMs use area under the curve (AUC) modelling to derive the proportion of patients in each health state[63, 64]. Analyses of AUC in this context typically use OS and PFS data to estimate the proportion of patients who are progression-free, progressed, or have died[65], and assume that patients can only progress forward through the health states (Figure 3).

The use of the PSM approach in reimbursement submissions for oncology medicines has been criticised, especially where clinical trial data are immature, and benefit is extrapolated over a much longer period beyond the duration of the studies [63, 65, 66]. Because PSM models typically do not take into account other, surrogate endpoints that may be impacted by treatment, the reliability of extrapolating immature data over the long-term may be less certain [64]. The NICE Decision Support Unit recommends that "state transition modelling should be used alongside the [PSM] approach to assist in verifying the plausibility of [PSM] extrapolations and to address uncertainties in the extrapolation period, even if this is only plausible for the pivotal trial" [64].

State-transition models

STMs differ to PSMs because the number of people moving between health states is determined using transition probabilities. Health states are related to each other, for example,

progression is linked to death, as opposed to PSMs where outcomes are modelled independently of one another [64, 65]. In STMs, the proportion of patients that are progression-free, progressed or dead is determined by the probability of transitioning between each health state (Figure 3). STMs include both cohort Markov models and individual patient microsimulation (e.g., Monte Carlo simulation) models[67]. STMs require post-progression data to estimate the transition probabilities for patients in the progressive disease health state, an endpoint that is not routinely reported in clinical trials and would require access to individual patient data to derive in a post-hoc analysis[64, 65]. The long-term uncertainty associated with immature survival data for cell and gene therapies warrants exploration of the impact of model structure on incremental cost-effectiveness, particularly when it comes to extrapolating survival benefit over a lifetime horizon.

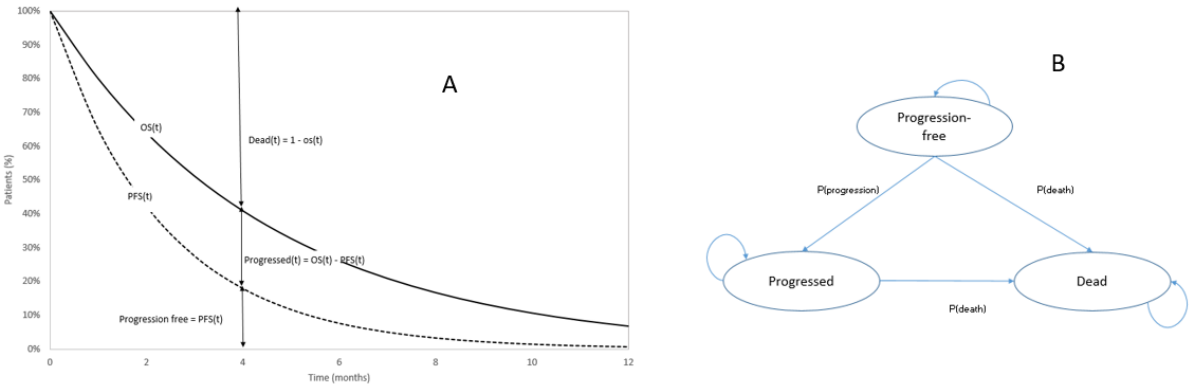


Figure 3 (A) Structural comparison of a 3-health state partitioned survival model and (B) a state-transition State transition model

Source: Adapted from Bluemont et al; Woods et al [31, 33]
OS denotes overall survival; P, the probability of moving between health states; PFS, progression-free survival; t, time.

Discrete event simulation

DES models are less commonly utilised compared with PSM and STM in economic evaluations of healthcare interventions, potentially due to their perceived complexity and lack of transparency[68], and have more traditionally been applied when there is a need to incorporate wait-times or queuing, usually associated with surgical interventions[62, 69]. DES can capture the interaction

between individual patients or other entities using a stochastic approach, whereby the movement of individual patients through the model is event-driven, relying on probability distributions to determine the time to the next event, therefore there is no fixed cycle length[69, 70]. This approach allows for more complex systems to be modelled and can more easily capture changes over time[69, 70]. DES may be an appropriate modelling technique for CAR-T due to its relatively complex manufacturing process compared with conventional medicines. There is potential for variability in the time taken to manufacture CAR-T cells, due to the logistics of shipping cells to a manufacturing facility, which may be located in a different country[71], as well as the potential for capacity constraints as manufacturing sites may not be able to easily adjust to increases in demand.

Mixture-cure models

A mixture-cure model uses a statistical approach to modelling the survival probability of two groups of patients "cured" and "uncured" and may be applied when a treatment is considered to be curative for some patients[72]. The advantage of mixture-cure modelling over standard parametric models is the ability to incorporate a "turning point" in the survival extrapolation to more accurately represent the different hazard rate in each of the two groups, "cured" and uncured"[73]. The application of mixture-cure models was not explored further in this thesis, as immature survival data and a lack of external data makes identifying a "curative" group difficult and may lead to implausible results[74].

Aim and objectives

The overall aim of this research was to identify key areas of uncertainty in assessing the cost-effectiveness of cell and gene therapies and ascertain whether current methodological approaches to modelling cost-effectiveness, applied to conventional medicines, are appropriate in guiding HTA agencies, and ultimately governments, to make public funding decisions for cell and gene therapies in a timely way. To address this overarching question, the research was broken down into four key objectives, applied to the CAR-T therapy, tisagenlecleucel, for the treatment of children and young adults with relapsed or refractory ALL, as a case-study. The four key objectives were as follows:

1. Identify key sources of uncertainty in modelled economic evaluations of CAR-T considered by HTA agencies via a systematic search of agency websites (Chapter 2).
2. Design an economic model to assess the value of OBAs as a mechanism for managing long-term clinical and economic uncertainty, in terms of maintaining cost-effectiveness and overall financial impact (Chapter 3).
3. Incorporate CAR-T wait-time, defined as the period between leukapheresis and infusion of CAR-T cells, in a modelled economic evaluation using DES to assess the impact of a change in wait-time on cost-effectiveness (Chapter 4).
4. Conduct a comparison of different modelling techniques to understand the impact of structural uncertainty on cost-effectiveness and develop a framework for selecting the most appropriate approach for modelling the cost-effectiveness of cell and gene therapies (Chapter 5).

Thesis outline

Each manuscript has been incorporated as a Word document into the thesis. Typographical amendments have been made to the manuscripts from the published versions, including some changes to terminology and abbreviations to ensure consistency throughout the document.

Chapter 2 presents a literature review of cost-effectiveness analyses of CAR-Ts to addresses objective 1 of the research. The purpose of the review was to identify the key sources of uncertainty in cost-effectiveness analyses of CAR-Ts evaluated by HTA agencies, focusing on the use of CAR-T in young compared with older patients. The review identified differences in the results of modelled economic evaluations, particularly in terms of long-term benefit in young patients with ALL. The review also found that HTA recommendations for the funding of CAR-Ts were mostly conditional on ongoing follow-up and reviews of cost-effectiveness under MAPs. These findings were the basis for selecting young ALL patients as the population of interest for this research and informed the next phase of the research.

Chapter 3 presents an economic model designed to test the impact of different OBAs in alleviating cost-effectiveness uncertainty to address objective 2. While OBAs aim to address uncertainty associated with the translation of trial outcomes to longer-term clinical outcomes, the extent to which OBAs alleviate uncertainty over the longer term is largely unknown. A PSM based economic model was developed which linked achievement of a complete remission (CR), the outcome selected for the OBA in the case of tisagenlecleucel, to survival in young ALL patients who received that treatment. The results showed the impact on reducing cost-effectiveness uncertainty under different OBA scenarios was modest relative to other sources of uncertainty in the model, whereas the potential financial uncertainty of an OBA was high. These findings suggests that economic models need to be designed to test the impact of OBAs in addressing cost-effectiveness uncertainty before decisions are made to implement them.

Chapter 4 addresses objective 3 by using a DES model to evaluate the impact of CAR-T wait-time, defined as the time between leukapheresis and CAR-T infusion, when assessing the cost-effectiveness of tisagenlecleucel in young patients with ALL. CAR-T therapies are different to conventional oncology medicines, particularly in terms of their process of administration, therefore DES was selected as the modelling technique because of its ability to capture complex clinical pathways and capacity constraints. When CAR-T wait-time was extended, the benefit of tisagenlecleucel at a population level was substantially reduced, reflecting the poor survival outcomes for ALL patients who are relapsed or refractory to multiple prior therapies. Total cost was also reduced due to fewer patients proceeding to infusion, thereby reducing the cost-effectiveness ratio. This highlights the importance of capturing CAR-T wait-time in an economic evaluation as it has implications for how payment arrangements can be structured to incentivise faster turn-around times for infusion.It also provides an example for how economic evaluations for next-generation, 'rapid', CAR-Ts (which utilise streamlined manufacturing processes to shorten the time between acquisition of patients' cells, their subsequent modification and return to the patient for infusion), may be designed to capture the value of reduced manufacturing time.”.

Chapter 5 addresses objective 4 by comparing three different model types to assess the cost-effectiveness of tisagenlecleucel in young ALL patients. An STM was developed and compared against the PSM and DES models described in the preceding chapters. PSM is the most common approach used in economic evaluation of oncology medicines, although may not be the most appropriate technique in evaluating the cost-effectiveness of cell and gene therapies, due to their complex manufacturing process, early phase data and high upfront cost. Although model structure did not meaningfully impact base-case results, 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-time and substantially reduce the benefit of CAR-T. The greater flexibility of the DES structure makes it an important tool for decision makers, so that major drivers of uncertainty can be considered when making funding decisions for these therapies, albeit more data intensive.

Chapter 6 is the discussion and conclusion to this work, summarising the key findings, implications for HTA and decision-makers, limitations of the research and areas for further work.

Chapter 2: HTA review of CAR-Ts

Gye A, De Abreu Lourenco R, Goodall S. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared with Older Patients. Value in Health. 2021;25(1):47-58. doi:10.1016/j.jval.2021.07.008

Abstract

Objectives: The objective of this review was to identify sources of variability in cost-effectiveness analyses of CAR-Ts (tisagenlecleucel and axicabtagene ciloleucel) evaluated by HTA agencies, focusing on younger versus older patients.

Methods: HTA evaluations in young ALL and adult DLBCL patients were included from Australia, Canada, England, Norway and the US. Key clinical evidence, economic approach, and outcomes (costs, QALYs and ICERs) were summarised.

Results: Fourteen HTA evaluations were identified (5 ALL, 9 DLBCL [4 tisagenlecleucel, 5 axicabtagene ciloleucel]). Analyses were naive comparisons of prospective single-arm studies for CAR-T versus retrospective cohort studies for the comparators. Key clinical evidence and economic model approaches were generally consistent by therapy and indication, although outcomes varied. Notably, incremental QALYs varied substantially in ALL (3.67 - 10.6 QALYs gained), whereas variation in DLBCL was less (1.21 - 1.97 [tisagenlecleucel], 1.97 - 3.40 [axicabtagene cilolceucel]). Discounting of costs and outcomes varied, with the highest QALYs generated for tisagenlecleucel in ALL (10.95) associated with the lowest discount rate (1.5%) and vice-versa (4.97 QALYs; 5% discount rate). The approach to extrapolation of OS data varied, even where the same empirical data were used.

Conclusion: Modelled, long-term treatment benefit in young patients may be associated with greater uncertainty compared with adults, due to potential life-long benefits with cell and gene therapies. This reflects the methodological challenges identified by HTA agencies associated with single-arm, short-term studies.

Highlights

- To our knowledge, this is the only review to identify sources of variability in cost-effectiveness analyses of CAR-Ts evaluated by HTA agencies, focusing on technologies in younger versus older patients. This review considers a number of major HTA agencies and provides a detailed comparison of the methodological approaches and results considered by each agency, that were the basis for decision-making.
- Key clinical evidence and economic models considered by each HTA agency were similar, although, the modelled benefit in terms of QALYs gained varied substantially by HTA agency in young ALL patients. The high variability in modelled benefit of tisagenlecleucel in young patients suggests a need for alternative approaches to assessing value for money, where evidence is limited and there is potentially substantial benefit, although further investigation is needed to validate this.

Introduction

Regulatory approvals for cell and gene therapies have been granted based on evidence from single-arm trials and surrogate outcomes, similar to orphan drugs for the treatment of rare diseases. However, subsequent reimbursement of cell and gene therapies may present an additional, unique set of issues, provoking concerns around how current HTA methodologies are applied to these treatments. A recent analysis of clinical trial pipeline data suggests that there may be 40 to 50 cell and gene therapies launched by 2030, with 12 in the next 5 years, and half of all launches are expected to be for the treatment of B-cell lymphomas and leukaemia[16]. This emphasises a need to understand whether HTA methodologies and systems need to adapt to accommodate these emerging therapies.

Cell and gene therapies represent potentially curative technologies that work using different techniques to repair or replace a defective gene[6]. Currently available gene replacement therapies use vectors to incorporate the new gene into the DNA of the cells which can occur in vivo or ex vivo[6].

In vivo gene therapy is administered directly into the body[3]. Voretigene neparvovec was the first gene replacement therapy to receive regulatory approval in the US in 2017 for vision loss[7], and more recently onasemnogene abeparvovec for SMA[8]. Ex vivo gene replacement occurs outside the body in cells isolated from the patient, and modified cells can then be selected and transduced, then reintroduced into the body via autologous transplant[3]. Ex vivo cell and gene therapies registered globally include the CAR-Ts; tisagenlecleucel for young ALL and adult DLBCL, and axicabtagene ciloleucel for DLBCL.

An issue frequently raised in the literature is the uncertainty inherent in interpreting an ICER generated from the extrapolation of short-term outcomes to long-term effectiveness[1, 66, 75, 76]. Although not a new issue, particularly for oncologic medicines, it is one arguably exacerbated for cell and gene therapies due to their use in rare, life threatening conditions, often in young patients[1]. Several key HTA bodies have sought to assess whether changes to their current HTA processes are needed for consideration of cell and gene therapies. In the UK, NICE commissioned a mock appraisal to consider a hypothetical CAR-T in paediatric ALL[9]. Although a need for an alternative assessment pathway was not identified by NICE (Text Box 1), there are different pathways within the existing NICE system that may provide enough flexibility to accommodate cell and gene therapies, such as the Highly Specialised Technologies (HST) program and the Cancer Drugs Fund [77].

Text Box 1: NICE review findings from the assessment of regenerative medicines and cell therapy products

(1) Current methods and processes are suitable for cell and gene therapies.
(2) Quantifying potential uncertainty is an important consideration in the decision-making process.
(3) Innovative payment methodologies will be important where there is a both a high level of uncertainty (due to immature evidence) and high expected patient benefits.
(4) Analyses are highly sensitive to discounting.

In the US, the Institute for Clinical and Economic Review undertook an assessment of the challenges associated with economic evaluation of cell and gene therapies, and made a number of revisions to its value assessment framework (Text Box 2)[78].

Text Box 2: Institute for Clinical and Economic Review: Adapted value assessment methods for high impact "single and short-term therapies"

(1) Set criteria to identify treatments eligible for an adapted assessment method.
(2) Cure proportion modelling as the standard approach for fitting survival data, with the use of other approaches in scenario analyses
(3) Additional elements of value, including the "value of hope" and "option value" using qualitative methods
(4) No change to its reference case 3% discounting to costs and benefits
(5) Sharing of health system savings using a different approach to incorporating cost offsets from a new treatment

CADTH undertook a survey of international HTA organisations and a literature review on cell and gene therapies[79], highlighting the issue of the temporal gap between achieving regulatory approval and securing funding after HTA evaluation due to the lack of long-term RCTs. A revised process has since been established by CADTH for cell and gene therapies [80], although the change is process related only, and the approach to assess cost-effectiveness remains the same.

Common gaps identified by the three agencies were predominantly related to a need to quantify uncertainty to assist decision-making; to consider alternative payment arrangements; and address budget impact concerns. The impact of discounting was raised by NICE and the Institute for Clinical and Economic Review, although no changes to discount rates were proposed. Following these reviews, CAR-Ts have undergone HTA assessments globally to determine eligibility for public funding for paediatric ALL (tisagenlecleucel) and adult DLBCL (tisagenlecleucel and axicabtagene ciloleucel).

The objective of this review was to identify potential sources of variability in cost-effectiveness analyses of CAR-Ts evaluated by HTA agencies, focusing on younger versus older patients, to identify key methodological challenges encountered by decision makers.

Methods

Search strategy

A search for HTA evaluations of CAR-Ts tisagenlecleucel and axicabtagene ciloleucel was conducted between May – July 2020. Other cell and gene therapies were not considered because they were in the early phases of registration and reimbursement. HTA agencies selected because they either represent large jurisdictions or are well established and have been included in previous HTA reviews[81, 82]. The Institute for Clinical and Economic Review, while it does not formally advise on the economic value of health care interventions to Government, was included because it was considered to influence Government policy and healthcare funding decisions. HTA evaluations were excluded if publications were not in English, or where limited information was published on cost-effectiveness.

Data extraction

Data extracted for review and comparison across the HTA agencies included:

1. Intervention and comparator
2. Patient population
3. Key clinical evidence
4. Economic model structure
5. Methods of extrapolation of OS
6. Source of utility data
7. Time horizon and discount rates
8. Outcomes of the economic evaluation (costs, QALYs and ICERs)
9. Main methodological challenges identified by the HTA agency
10. The agency's final recommendation

For each therapy, only the final assessment that was the basis of the funding recommendation was included; prior submissions for the same therapy considered more than once

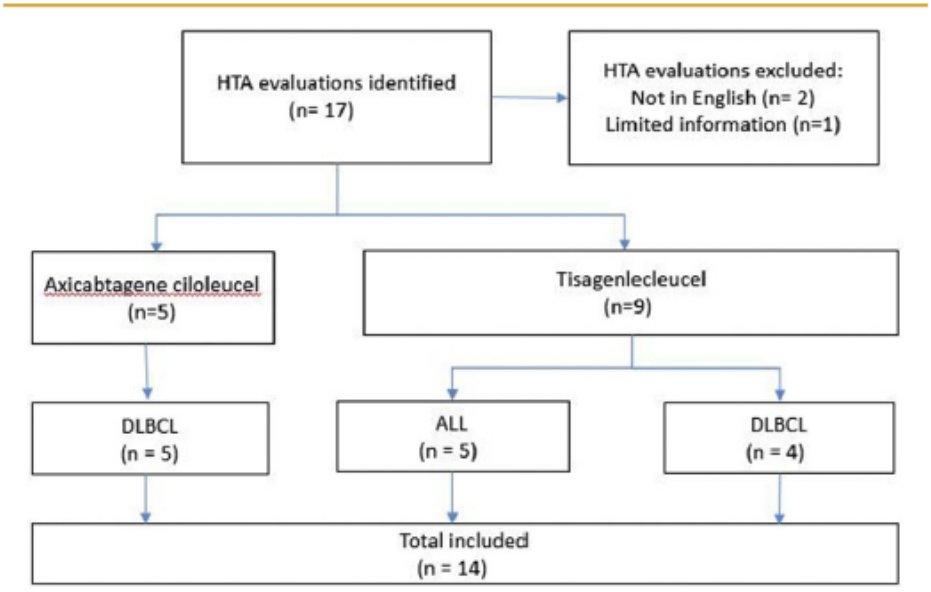
by an HTA agency were not reviewed. Information was extracted from the base case analysis, after any adjustments had been made by the evaluators or reviewers, and not from the original approaches or results of the economic evaluations put forward by the sponsor. The method for performing the systematic review followed the approach outlined in the PRISMA Guidelines [83]. The number of HTA evaluations identified were reported in the format of a PRISMA Flow Diagram. Relevant information was extracted and summarised descriptively. Where outcomes data (costs, QALYs and ICERs) were available, these data were collated into an Excel workbook, and currencies were converted to US dollars, using Reserve Bank of Australia (RBA) exchange rates on 20 November 2020, for comparison.

Results

Search results

A total of 17 HTA evaluations were identified. Three evaluations were excluded from further review because they were not published in English (Dental and Pharmaceutical Agency, Sweden [TLV] and National Health Care Institute, Netherlands [ZiN]), or published only limited information[2] (Scottish Medicines Agency [SMC]). A total of 14 HTA evaluations for CAR-T therapy were identified from the HTA agencies CADTH, Institute for Clinical and Economic Review, MSAC in Australia, NICE and the Norwegian Medicines Agency (NoMA, Figure 4).

2 For tisagenlecleucel, the structure and key assumptions of the economic model and model outcomes were not published. For axicabtagene ciloleucel, details of revised economic model, including assumptions and outcomes considered in the final recommendation were not reported.



ALL indicates acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 4 PRISMA flow chart of the number of HTA reviews by product and indication

Clinical evidence

No direct comparative clinical evidence was available for any of the therapies in either indication; consequently, all evaluations were based on naive comparisons of prospective single-arm studies for CAR-Ts versus retrospective cohort studies for the comparators (Table 1).

Evidence for tisagenlecleucel in ALL was from phase II single-arm trials (ELIANA and ENSIGN)[23, 84] and a phase I/IIA safety and feasibility study (B2101J)[84]. NICE considered it appropriate to pool data from all three studies, whereas MSAC and NoMA included ELIANA and ENSIGN only. CADTH did not consider the pooling of data appropriate due to differences in dosing and study designs, and only ELIANA was included in comparative analysis.

Blinatumomab was considered the main relevant comparator to tisagenlecleucel in ALL by CADTH, MSAC and NICE, with evidence from a single-arm post-hoc analysis by Von Stackelberg [85]. In contrast, the Institute for Clinical and Economic Review considered clofarabine as the comparator with evidence from a single-arm post-hoc analysis by Jeha [86]. NoMA considered clofarabine in

combination with etoposide and cyclophosphamide as the comparator for tisagenlecleucel, with evidence sourced from Hijiya et al[87].

Evidence for tisagenlecleucel in DLBCL was from a phase II single-arm trial (JULIET)[88]. The UPENN trial[89] was considered supplementary evidence due to small patient numbers, albeit longer follow-up time. Only the JULIET trial was considered in comparative analysis, with the exception of NICE who considered the pooled JULIET and UPENN data. A mixed salvage chemotherapy regimen was consistently considered the main relevant comparator, although the source of evidence differed; CADTH and MSAC considered the SCHOLAR-I[90] trial to be most relevant, whereas NICE and NoMA preferred the CORAL study[91].

Evidence for axicabtagene ciloleucel was from a phase II single-arm trial (ZUMA-1)[92]. A mixed salvage chemotherapy regimen was considered the relevant comparator to axicabtagene ciloleucel, and SCHOLAR-I was the only source of comparative evidence considered.

Unadjusted naive comparisons of the single arm studies were generally considered the most appropriate approach to comparative analysis. One exception was NoMA, basing its recommendation for axicabtagene ciloleucel on a propensity score-adjusted analysis, despite the imbalances in patient characteristics. The Institute for Clinical and Economic Review did not consider it appropriate to conduct any formal comparisons.

Overall, the comparative clinical evidence for both therapies in both indications was considered uncertain in terms of the long-term outcomes (event-free survival [EFS] and OS) due to non-comparative trial design, small patient numbers and the immaturity of the long-term outcomes.

Table 1 Summary of clinical evidence and interpretation from the HTA evaluations

Agency	Comparator	Evidence	Comparative analysis	Interpretation of the clinical evidence
Tisagenlecleucel, paediatric ALL				
CADTH[93, 94]	Blinatumomab	ELIANA, ENSIGN & B2101J vs. Stackelberg et al	Naive comparison using ELIANA only. CADTH considered it inappropriate to pool data due to differences in dosing and study designs.	There is uncertainty in the clinical evidence due to the lack of long-term follow-up data, single-arm pivotal trial and small patient numbers in the studies.
ICER[95]	Clofarabine	ELIANA, ENSIGN & B2101J vs. Jeha et al	No formal statistical comparisons undertaken	The estimated health benefit is substantial, although the magnitude is uncertain due to non-comparative trials of short duration.
MSAC[14]	Blinatumomab	ELIANA, ENSIGN & B2101J vs. Stackelberg et al	Naive comparison using pooled ELIANA & ENSIGN data.	Tisagenlecleucel shows promising rates of remission, although noted clinical uncertainties (due to single-arm studies, small patient numbers, heterogeneous patient

				characteristics and short follow-up).
NICE[42, 96]	Blinatumomab	ELIANA, ENSIGN & B2101J vs Stackelberg et al	Naive comparison using pooled ELIANA, ENSIGN & B2101J data.	Tisagenlecleucel is clinically effective, but lack of comparative data a challenge; clinical evidence beyond 30 months uncertain due to small patient numbers and differences in trial populations. No robust evidence that tisagenlecleucel is curative.
NoMA[97]	Clofarabine + etoposide/cyclophosphamide	ELIANA, ENSIGN & B2101J vs Hijiya et al	Naive comparison using pooled ELIANA & ENSIGN data.	Tisagenlecleucel appears to have superior efficacy versus the comparator, although the relative treatment effect cannot reliably be established due to data limitations.
Tisagenlecleucel, adult DLBCL				
CADTH[93, 98]	Salvage chemotherapy	JULIET and UPENN vs SCHOLAR-I	Naive comparison using JULIET only.	There is uncertainty in the clinical evidence due to the lack of long-term follow-up data, single-arm pivotal trial and small patient numbers in the studies.

MSAC[99]	Salvage chemotherapy	JULIET and UPENN vs SCHOLAR-I	Naive comparison using JULIET only.	ESC considered claims of superior effectiveness and uncertainty are unsubstantiated due to immature survival data. MSAC acknowledged that tisagenlecleucel is clinically effective in some patients.
NICE[43, 100]	Salvage chemotherapy	JULIET and UPENN vs CORAL	Naive comparison using pooled data.	Tisagenlecleucel benefit uncertain due to single-arm study design and immature survival data.
NoMA[101]	Salvage chemotherapy	JULIET vs CORAL	Naive comparison using JULIET only, with censoring of early deaths in CORAL study.	Analysis considered uncertain due to single-arm study design, small patient numbers short follow-up.
Axicabtagene ciloleucel, adult DLBCL				
CADTH[102, 103]	Salvage chemotherapy	ZUMA-I vs SCHOLAR-I	Adjusted indirect comparison using propensity score matching.	Long-term benefit of axicabtagene ciloleucel uncertain due to small population size and lack of head-head comparisons or any randomization design.

ICER[95]	Salvage chemotherapy	ZUMA-I vs SCHOLAR-I	No formal statistical comparisons undertaken.	The estimated health benefit is substantial, although the magnitude is uncertain due to non-comparative, single arm trials of short duration.
MSAC[52]	Salvage chemotherapy	ZUMA-I vs SCHOLAR-I	Naive comparison.	Axicabtagene ciloleucel was most likely superior to salvage chemotherapy although the evidence had a high risk of bias.
NICE[44, 104]	Salvage chemotherapy	ZUMA-I vs SCHOLAR-I	Adjusted indirect comparison.	Axicabtagene ciloleucel is clinically effective but the lack of comparative data made the assessment of comparative effectiveness challenging.
NoMA[105]	Salvage chemotherapy	ZUMA-I vs SCHOLAR-I	Adjusted indirect comparison using propensity score matching,	Estimated gain in overall and quality adjusted survival uncertain due to lack of comparative data, small sample sizes and short follow-up.

Abbreviations: ALL, acute lymphoblastic leukaemia CADTH, Canadian Agency for Drugs and Technologies in Health; DLBCL, diffuse large B cell lymphoma; ICER, Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medicines Agency

Economic analyses

All economic models were considered from a healthcare system perspective and the majority structured using a PSM consisting of three health states; PFS, progressed and dead (Table 2). One exception to the PSM structure was the use of a four health-state Markov model applied to the axicabtagene ciloleucel arm only in the submission to MSAC to include a "cured" health state, which according to MSAC assumed a large proportion of patients treated with axicabtagene ciloleucel would be cured, making the model insensitive to changes in survival extrapolation[52]. Additionally, the Institute for Clinical and Economic Review and NICE models for tisagenlecleucel in ALL and DLBCL included a decision tree preceding the PSM to take into account eligible patients who did not proceed to the infusion stage (due to manufacturing failure, an adverse event or death).

The approach to extrapolation of the OS data beyond the duration of the trials varied. For the tisagenlecleucel extrapolation in ALL, the Institute for Clinical and Economic Review, MSAC and NoMA concluded that a lognormal distribution was the most appropriate, whereas CADTH considered a weighted average parametric equation using all plausible survival functions to be the most reliable. CADTH, the Institute for Clinical and Economic Review, MSAC and NoMA applied long-term mortality from 5 years adjusted for ALL long-term survival from the literature. The Institute for Clinical and Economic Review applied long-term all-cause mortality based on the general population (unadjusted) from 5 years. NICE applied a mixture cure model (log-logistic distribution) with long-term survivor mortality applied at 2 and 5 years. For the extrapolation of the comparator arm, generally the same approach was applied as for the tisagenlecleucel arm, with the exception of NoMA where a spline model was used for the comparator.

For tisagenlecleucel in DLBCL, spline extrapolation was consistently applied to the OS data, followed by long-term DLBCL survivor mortality, applied from 3 years by CADTH, Institute for Clinical and Economic Review, MSAC, and NoMA, and from 2 and 5 years by NICE. For the comparator arm, different approaches were used including a weighted average parametric and flexible cubic-spline model applied to the SCHOLAR-I study (CADTH and MSAC), and a gompertz extrapolation of the

CORAL study (NICE and NoMA). For axicabtagene ciloleucel, a variety of extrapolation methods were applied to the ZUMA-1 trial data, including mixture cure (lognormal), log logistic and spline models, followed by long-term mortality adjusted for DLBCL long-term survivors (CADTH, NICE, NoMA), and all-cause mortality (Institute for Clinical and Economic Review). Similarly, different extrapolation approaches were applied to the comparator data from SCHOLAR-1.

All economic analyses were based on a lifetime horizon. Utility data were sourced from a combination of clinical trials and published literature (Kelly et al[106] [ALL] and Chen et al[107] [axicabtagene ciloleucel only]). Discounting of costs and benefits was at the standard discount rates for each jurisdiction, varying from 1.5% (CADTH) to 5% (MSAC). NICE considered the use of a lower discount rate for costs and benefits (1.5%) in its appraisals, although concluded that there was no robust evidence that the therapies were curative, and therefore recommended the use of a 3.5% discount rate for the reference case [42, 44]. In sensitivity analyses, the Institute for Clinical and Economic Review found that cost-effectiveness of tisagenlecleucel in paediatric ALL and axicabtagene ciloleucel in adult DLBCL was highly sensitive to variations in the discount rate (1.5% - 5%)[95].

Table 2 Approach to the economic analyses in each HTA evaluation

Agency	Perspective	Model population	CE model structure	OS extrapolation, CAR-T	OS extrapolation, Comparator	Utilities	Time horizon	Discounting
Tisagenlecleucel, paediatric ALL								
CADTH[93, 94]	Healthcare system	ELIANA vs Stackelberg et al	3-state PSM	Parametric (weighted average of all plausible functions) until year 5, followed by long-term survivor mortality.	Parametric (weighted average of plausible functions) until year 5, followed by long-term survival mortality.	ELIANA trial	Lifetime (70 years)	1.5% costs and benefits
ICER[95]	Healthcare system	Pooled ELIANA and ENSIGN vs Jeha et al 2006	3-state PSM with decision analysis to account for non-infused patients	Parametric (lognormal) extrapolation with knot[3] at 2.5 years, then all-cause mortality from 5 years.	Parametric (lognormal) extrapolation with knot at 1.2 years, then all-cause mortality from 5 years.	Kelly et al	Lifetime (NR)	3% costs and benefits
MSAC[14]	Healthcare system	Pooled ELIANA and ENSIGN trials vs Stackelberg et al	3-state PSM	Parametric (lognormal) until year 5, followed by	Parametric (lognormal) until year 5, followed by	ELIANA trial	Lifetime (88 years)	5% costs and benefits

[3] "Knot" refers to the point within a data range where adjacent data segments are joined together 108. Perperoglou A, Sauerbrei W, Abrahamowicz M, Schmid M. A review of spline function procedures in R. *BMC Med Res Methodol*. Mar 6 2019;19(1):46. doi:10.1186/s12874-019-0666-3

				long-term survivor mortality.	long-term survivor mortality.			
NICE[42, 96]	Healthcare system	Pooled ELIANA and ENSIGN trials vs Stackelberg et al	3-state PSM with decision analysis to account for non-infused patients	Mixture cure model (loglogistic distribution) with cure points at 3 or 5 years, followed by long-term survivor mortality.	Mixture cure model (loglogistic distribution) followed by long-term survivor mortality.	ELIANA trial and Kelly et al	Lifetime (88 years)	3.5% costs and benefits
NoMA[97]	Healthcare system	Pooled ELIANA and ENSIGN trials vs Hijiya et al	3-state PSM	Parametric (lognormal) until year 5, followed by long-term survivor mortality.	Spline model with 2 knots until year 5, followed by long-term survivor mortality	ELIANA trial and Kelly et al	Lifetime (88 years)	4% costs and benefits
Tisagenlecleucel, adult DLBCL								
CADTH[93, 98]	Healthcare system	JULIET and UPENN vs SCHOLAR-I	3-state PSM	Spline model with 2 or 3 knots until 3 years, followed by long-term survivor mortality.	Parametric (weighted average), until 3 years, followed by long-term survivor mortality.	JULIET trial	20 years	1.5% costs and benefits
MSAC[99]	Healthcare system	JULIET and UPENN vs SCHOLAR-I	3-state PSM	Spline model with 1 or 2 knots until 3	Flexible cubic spline, followed by long-	JULIET trial	Lifetime (50 years)	5% costs and benefits

				years, followed by long-term survivor mortality.	term survivor mortality.			
NICE[43, 100]	Healthcare system	JULIET and UPENN vs CORAL	3-state PSM with decision analysis to account for non-infused patients	Spline model with 1 knot until point of cure (2 to 5 years) followed by long-term survivor mortality.	Parametric (gompertz)	JULIET trial	Lifetime (46 years)	3.5% costs and benefits
NoMA[101]	Healthcare system	JULIET vs CORAL	3-state PSM	Spline model with 2 knots until point of convergence of PFS and OS (3 years), followed by long-term survivor mortality.	Parametric (gompertz), constrained by all-cause mortality.	JULIET trial	Lifetime	4% cost and benefits
Axicabtagene ciloleucel, adult DLBCL								
CADTH[102, 103]	Healthcare system	ZUMA-1 vs. SCHOLAR-1	3-state PSM	Mixture cure model (lognormal), followed by long-term survivor mortality (cure point redacted)	Mixture cure model (lognormal), followed by long-term survivor mortality (cure point redacted).	ZUMA-1	Lifetime (44 years)	1.5% costs and benefits

ICER[95]	Healthcare system	ZUMA-1 vs. SCHOLAR-1	3-state PSM with decision analysis to account for non-infused patients	Parametric (lognormal) with knot at 2 years, followed by all-cause mortality from 5 years.	Parametric (loglogistic) with knot at 1.2 years, followed by all-cause mortality from 5 years.	Chen et al (2017)	Lifetime (NR)	3% costs and benefits
MSAC[52]	Healthcare system	ZUMA-1 vs. SCHOLAR-1	3-state PSM (SCR arm) vs 4-state Markov (axicabtagene ciloleucel arm)	Assumed a cure portion based on the proportion of patients in PFS. No further details reported.	NR	NR	Lifetime (44 years)	5% costs and benefits
NICE[44, 104]	Healthcare system	ZUMA-1 vs. SCHOLAR-1	3-state PSM with decision analysis to account for non-infused patients	Parametric (loglogistic) until point of convergence of OS and PFS (4.2 years), followed by long-term survivor mortality.	Parametric (gompertz)	NR	Lifetime (44 years)	3.5% costs and benefits

NoMA[105]	Healthcare system	ZUMA-1 vs. SCHOLAR-1	3-state PSM	Spline model with 2 knots until point of convergence of PFS and OS (3 years), followed by long-term survivor mortality.	Spline model with 1 knot, constrained by all-cause mortality.	JULIET trial	Lifetime (NR)	4% cost and benefits

Abbreviations: ALL, acute lymphoblastic leukaemia; CADTH, Canadian Agency for Drugs and Technologies in Health; DLBCL, diffuse large B cell lymphoma; CE, cost-effectiveness; ERG, economic review group; ICER, Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medicines Agency; NR, not reported; PS, propensity score; PFS, progression-free survival; PSM, partitioned survival model; OS, overall survival.

Results of the economic evaluation

In paediatric ALL, ICERs ranged from $39,146 (NICE) up to $98,450 (MSAC), approximately a 2.5 - fold difference (Table 3). Consistent with the variation in ICERs, reported incremental costs and QALYs also varied, with QALYs in particular varying substantially. The highest number of incremental QALYs gained for tisagenlecleucel was 10.6 (CADTH) and the lowest was 3.67 (NoMA). This can be explained in part by the base case QALYs assigned to the comparator which were lowest for CADTH (0.35) and highest for NoMA (3.14 - 3.44). The lowest number of total QALYs assigned to tisagenlecleucel was 4.97 (MSAC). Incremental costs ranged from $226,091 (NoMA) - $443,233 (CADTH), where reported.

For tisagenlecleucel in DLBCL, the ICERs ranged from $57,046 (NICE) to $268,415 (NoMA), approximately a 5-fold difference (Table 3), although incremental QALYs were reasonably consistent, ranging from 1.21 for NoMA up to 1.97 for CADTH. Incremental costs ranged from $84,868 (MSAC) to $340,050 (NoMA). For axicabtagene ciloleucel in DLBCL, ICERs ranged from greater than $66,346 (NICE; equivalent to the £50,000 threshold) up to $173,198 (CADTH) (Table 3). For axicabtagene ciloleucel, incremental QALYs ranged from 1.97 to 3.40, and incremental costs ranged from $304,495 to $462,043 (NoMA and Institute for Clinical and Economic Review), where reported.

Figure 5 shows the relationship between incremental costs, QALYs and ICERs by indication and CAR-T. The chart highlights the high variability in QALYs gained in paediatric ALL relative to adult DLBCL. Incremental costs were more widely distributed in adult DLBCL, with higher ICERs (represented by the size of the circle) relative to paediatric ALL.

Table 3 Results of the economic evaluations in each HTA evaluation

Agency	Costs (USD)			QALYs			ICER (USD)
	Tisagenlecleucel	Comparator	Incremental	Tisagenlecleucel	Comparator	Incremental	
Tisagenlecleucel, paediatric ALL							
CADTH[93, 94]	$611,945	$178,722	$433,223	10.95	0.35	10.60	$40,794
ICER[95]	$666,754	$337,256	$329,498	9.28	2.10	7.18	$45,871
MSAC[14]	NR	NR	$256,43 – $364,562	4.97	1.27	3.70	$69,280 - $98,450
[1]NICE[42, 96]	NR	NR	NR	NR	NR	NR	$39,146
[2]NoMA[97]	$455,898 -$522,838	$189,806	$226,091 – 333,032	7.12 – 8.06	3.44	3.67 – 4.62	$72,099 - $72,435
Tisagenlecleucel, adult DLBCL							
CADTH[93, 98]	$445,405	$126,208	$319,197	4.11	2.14	1.97	$162,275
MSAC[99]	NR	NR	$84,868 - $120,602	2.99	1.77	1.23	$69,280 - $98,450
[3]NICE[43, 100]	NR	NR	NR	NR	NR	NR	$57,046 - $73,516
[2]NoMA[101]	$299,355 - $406,523	$61,283 – $66,473	$238,072 - $340,050	3.62 – 4.31	2.41 – 3.07	1.21 – 1.25	$197,416 - $268,415
Axicabtagene ciloleucel, adult DLBCL							
CADTH[102, 103]	$479,545	$81,505	$398,040	4.47	2.17	2.30	$173,198
ICER[95]	$616,927	$154,884	$462,043	5.87	2.48	3.40	$136,078
MSAC[52]	NR	NR	NR	NR	NR	NR	NR
NICE[44, 104]	NR	NR	NR	NR	NR	NR	>$66,346

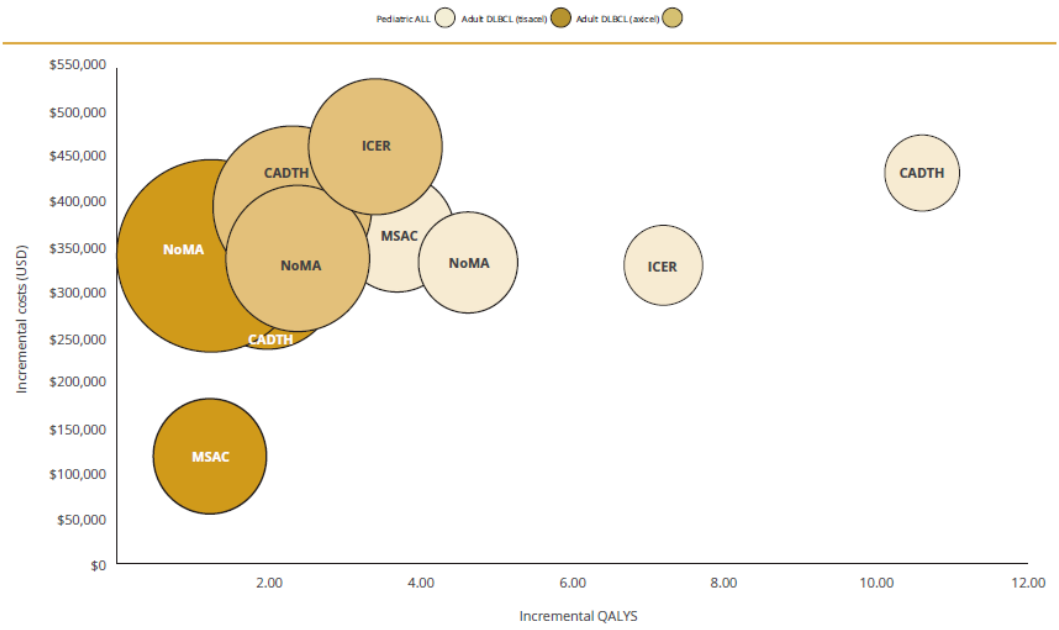
[2]NoMA[105]	$365,520 - $397,630	$60,359 – $61,026	$304,494 - $337,271	4.93 – 5.32	2.95 – 2.96	1.97 – 2.36	$142,690 – $154,590

Abbreviations: ALL, acute lymphoblastic leukaemia; CADTH, Canadian Agency for Drugs and Technologies in Health; DLBCL, diffuse large B cell lymphoma; ICER, incremental cost-effectiveness ratio; ICER, Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medicines Agency; NR, not reported; QALY, quality adjusted life year

[1]The ERG's probabilistic base case ICER compared with blinatumomab was £29,501 per QALY gained and does not take into account discounts from the list price for blinatumomab (comparator) and tocilizumab (used to treat cytokine release syndrome). The Committee concluded the most plausible ICERs were > £30,000.

[2]Range based on ITT population and modified ITT population (modified ITT excludes non-infused patients)

[3]Range based on 2 and 4-year cure points, both considered plausible by the Committee.



CADTH indicates Canadian Agency for Drugs and Technologies in Health; ICER, incremental cost-effectiveness ratio; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medicines Agency; QALY, quality-adjusted life-year.

Figure 5 Scatter plot displaying the relationship between incremental costs, QALYs, and ICERs by indication and CAR-T therapy.

Note. Circle size is proportional to the ICER value; NICE data are not displayed because of lack of reporting of costs and QALYs. Where a range was reported, the higher value was included.
Note correction to abbreviation: ICER, denotes Institute for Clinical and Economic Review.

Pricing and managed entry recommendations

Publication of manufacturer prices for CAR-Ts was limited. Where reported, prices for CAR-Ts (excluding associated hospital costs or mark-ups) were in the range of $342,959 to $575,000 (Table 4). Following a review of cost-effectiveness, CADTH, NICE and MSAC specified a requirement for price reductions (up to 83%). The majority of HTA agency recommendations included a requirement for longer-term follow-up data from clinical trials as well as additional data collection via patient registries for use in reassessment of cost-effectiveness.

Table 4 Pricing and managed entry recommendations

Agency	Manufacturer price (USD)[1]	Recommended price discount	Managed entry arrangement
Tisagenlecleucel, paediatric ALL			
CADTH[93]	NR	Recommended on the condition of at least 10% price reduction.	Collection of a defined set of outcomes data via a national patient registry to generate real world evidence for use in reassessment of longer-term effectiveness, safety and cost-effectiveness.
ICER[95]	$575,000	None	None
MSAC[14]	NR	NR	No payment for an unsuccessful infusion; limit of one successful CAR-T infusion per lifetime; full review of clinical effectiveness, cost-effectiveness and budget no later than 2 years post commencement of public subsidy.
NICE[42, 109]	$374,193	Confidential price discount required.	Further data collection from clinical trials and patient registries[2], including data to determine the rate of subsequent stem cell transplants followed by a NICE reappraisal on trial completion.
NoMA[97]	$342,959	NR	NR
Tisagenlecleucel, adult DLBCL			
CADTH[93]	NR	At least 45% - 65% price reduction required to achieve an acceptable cost-effectiveness threshold.	Collection of a defined set of outcomes data via a national patient registry to generate real world evidence for use in reassessment of longer-term effectiveness, safety and cost-effectiveness.
MSAC[99]	NR	NR	No payment for an unsuccessful infusion; limit of one successful CAR-T infusion per lifetime; data on the use of tisagenlecleucel to be collected via a patient registry;

			progress review at year 1 to assess appropriateness of patient eligibility criteria and patient numbers, followed by a full review of clinical effectiveness, cost-effectiveness and budget impact based on all data and information available at the time no later than 2 years post commencement of public subsidy.
NICE[43, 110]	$374,193	Confidential price discount required.	Further data collection from clinical trials and patient registries[3] followed by NICE reappraisal on trial completion. Outcomes for data collection include overall survival, progression-free survival and intravenous immunoglobulin use.
NoMA[101]	$342,959	NR	NR
Axicabtagene ciloleucel, adult DLBCL			
CADTH[102]	NR	At least 60% - 83% price reduction required to achieve an acceptable cost-effectiveness threshold.	Collection of a defined set of outcomes data via a national patient registry to generate real world evidence for use in reassessment of longer-term effectiveness, safety and cost-effectiveness.
ICER[95]	$373,000	None	Payment for responders only outcomes-based payment provided more favourable cost-effectiveness estimates.
MSAC[52]	NR	Price reduction of 40-45% required.	No payment for an unsuccessful infusion; limit of one successful CAR-T infusion per lifetime; data on the use of axicabtagene ciloleucel to be collected via a patient registry; progress review at year 1 to assess appropriateness of patient eligibility criteria and patient numbers, followed by a full review of clinical effectiveness, cost-effectiveness and budget impact based on all data and information available at the time no later than 2 years post commencement of public subsidy.
NICE[44, 111]	NR	Confidential price discount required.	Further data collection from clinical trials and patient registries[4], followed by NICE reappraisal. Five-year follow-up data from the pivotal trial and additional data on

			intravenous immunoglobulin use required, 3-year data become available. Key outcomes of interest include overall survival and progression-free survival, as well as intravenous immunoglobulin use in the real world.
NoMA[105]	$345,985	NR	NR

Abbreviations: ALL, acute lymphoblastic leukaemia; CADTH, Canadian Agency for Drugs and Technologies in Health; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B cell lymphoma; ICER, Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medicines Agency; NR, not reported.

[1]Does not include potential hospital mark-ups or associated hospital administration costs. Does not take into account any confidential price discounting.

[2]Sources of ongoing data collection include ELIANA (primary source), the UK bone marrow stem cell transplant registry, and other patient databases.

[3]Sources of ongoing data collection include JULIET (primary source), UPENN, and other patient databases.

[4]Sources of ongoing data collection include ZUMA-1 (primary source), other patient databases

Discussion

Clinical evidence and economic modelling

Clinical evidence for CAR-Ts assessed by each jurisdiction was from single-arm clinical trials of short duration (median follow-up 19.3 months to 27.1 months). Comparative analyses were performed against retrospective, observational studies mainly using unadjusted naive comparisons, as matched adjusted indirect comparisons or propensity score matching was generally considered inappropriate due to small patient numbers and lack of reporting of prognostic patient characteristics. All submissions were considered on the basis of similar economic modelling approaches, which is not necessarily unexpected given that submissions are lodged by the sponsor company, and sponsors are likely to adapt economic models to each country from a single globally developed model. However, approaches to extrapolation of the OS data beyond the trial period were varied, even when the same empirical data were used.

Results of the economic modelling

Despite the general consistency in clinical evidence and approach to the structure of the economic models, there was a large variation in ICERs. This is not an unusual finding because costs in particular are likely to vary across countries due to differences in pricing of therapies, hospital costs and disease management practices. In the case of CAR-Ts, costs may be substantially impacted by the use of intravenous immunoglobulin (IVIg) and the number of patients proceeding to stem cell transplant (SCT). It is recognized that different assumptions on resource measurement, parameter inputs and modelling assumptions may all be import drivers in variability in the costs observed, however this was not explored further due to limited reporting of disaggregated costs and assumptions However, it may be reasonable to assume that the benefit generated from the economic models in terms of QALYs gained would be similar, given the consistency in the clinical evidence and economic model structures. Differences in incremental QALYs were especially evident in paediatric ALL, ranging from 3.67 - 10.6 QALYs gained. By comparison, the magnitude of variation

in incremental QALYs in DLBCL was substantially less (1.21 - 1.97 and 1.97 - 3.40 for tisagenlecleucel and axicabtagene ciloleucel, respectively).

Sources of variability

The variability in ICERs, particularly QALYs, may be attributed to the different methods used to extrapolate OS data beyond the trial period. The variability in extrapolation methods used is likely a reflection of the limitations of the evidence. There is nothing to suggest certain preference for a particular type of extrapolation method, with HTA guidelines generally advising that an analysis of the hazards, AIC/BIC tests, biological plausibility and expert opinion should be used to assess the validity of survival curves[112 113].

Additionally, different discount rates applied by each HTA agency may contribute to the variability in QALYs. More QALYs are likely to be generated from an economic model that applies a lower discount rate, and this disproportionately affects a therapy with potential lifetime benefits versus the comparator where the benefit is substantially less[9]. For example, in paediatric ALL, CADTH applied a 1.5% discount rate and generated substantially more QALYs for tisagenlecleucel (10.95), compared with MSAC (4.97 QALYs gained) which applied a 5% discount rate. NICE in its consideration of the hypothetical CAR-T[9] concluded that the discount rate applied to costs and benefits had a very significant impact on the cost-effectiveness of CAR-T[114]. Others have raised the sensitivity of CAR-T to the discount rate in paediatric patients previously[115].

The high variability in QALYs was not limited to the CAR-T arm but was also apparent for the comparator arm in paediatric ALL (ranging from 0.35 for CADTH up to 3.44 for NoMA). This may largely be due to the different sources of comparative evidence considered by CADTH (SCHOLAR-I) and NoMA (CORAL), although the difference between CADTH and MSAC (0.35 versus 1.269 QALYs) was also substantial, despite the same source of comparative evidence. The different extrapolation approaches may be contributing to this variability, with CADTH considering a weighted average parametric approach and MSAC, a lognormal. If different discount rates had been a source of variability, we would expect to see the converse of that observed, with higher QALYs for the CADTH

comparator arm and lower QALYs for NoMA and MSAC. The highly variable results, particularly in paediatric ALL appear aligned with the conclusions drawn by NICE in the mock appraisal of a hypothetical CAR-T, where decision uncertainty increased where there was a combination of immature evidence but potentially very substantial patient benefits (due to a potential cure in a young, relapsed/refractory population). When the hypothetical CAR-T was assumed to be curative, the projected patient benefit was approximately 10 QALYs per patient , but this was combined with a very high level of uncertainty, and largely dependent on extrapolation from the available evidence[114].

It follows that where benefit is more modest, the potential for variability in modelled outcomes is reduced. This is reflected in the results generated from the economic models in DLBCL, where there is less potential to benefit in an older population with a median age of 56 - 58 (JULIET and ZUMA-1 trials)[88, 92], versus the greater potential to benefit in a young population with a median age of 11 years (ELIANA trial)[23], based on early trial evidence.

Other reviews have highlighted uncertainties associated with valuing CAR-Ts, although these have mainly looked at independent (not from the sponsor) cost-effectiveness analyses published in peer-reviewed journals[116 117]. In the most recent review[116], a wide range of QALYs was reported from the published literature, ranging from $37,000 per QALY gained to $184,000 per QALY gained for tisagenlecleucel in paediatric ALL, from $58,000 to $289,000 per QALY gained for axicabtagene ciloleucel in adult DLBCL, and from $168,000 - $223,000 per QALY gained for optimistic and conservative scenarios for tisagenlecleucel in DLBCL (from one study).

Addressing uncertainty

In assessing the value of cell and gene therapies, a number of publications have emphasised the need to deal with uncertainty [1,116]. Due to potential life-long benefits in high clinical need populations, accelerated regulatory approvals based on limited clinical data are being implemented to facilitate early registration[1, 9]. Ironically, where accelerated pathways are available, there is little

incentive for manufacturers to conduct long-term RCTs, once registration is granted, to address these uncertainties, consequently determining the long-term benefit will remain uncertain.

One of the key outcomes of NICE's consideration of the mock CAR-T appraisal was the need to develop innovative payment methodologies and share risk where there is a combination of high uncertainty due to the immaturity of the evidence but the potential for substantial patient benefits[114]. All HTA agency recommendations for CAR-Ts specify a need for longer-term follow-up data, and cost-effectiveness reviews, however there was no reporting of outcomes-based pricing arrangements, although the Institute for Clinical and Economic Review noted that cost-effectiveness estimates for axicabtagene ciloleucel were more favourable where payment was for responders only. Justification for model structures across all reimbursement submissions appear to have relied heavily on precedence originating from the mock CAR-T appraisal commissioned by NICE, and to some extent the review by the Institute for Clinical and Economic Review. There was no indication that alternative economic model structures (e.g., Markov vs partitioned survival) had been explored to address uncertainty due to limited follow-up.

All HTA agencies identified similar methodological challenges related to single-arm short-term studies; consequently, recommendations were conditional on the requirement for ongoing follow-up and reassessment of cost-effectiveness.

Limitations

A limited number of HTA evaluation were available for review because publications were not in English or reporting of data was limited. Additionally, information was not consistently reported, across agencies. The majority of submissions were sponsor driven, with the exception of the Institute for Clinical and Economic Review, and as such the clinical evidence and economic modelling approach was generally consistent. While this makes it easier to identify potential sources of variability, it also means that issues raised by each HTA agency were similar and may not translate to other cell and gene therapies. Furthermore, this review is specific to CAR-T for CD19 positive

relapse/refractory ALL and DLBCL, diseases which are curative for the majority of patients with front-line therapy, however the potential for cure with CAR-T in indolent lymphomas is still unknown[118].

Conclusion

The high variability in modelled benefit of tisagenlecleucel across HTA agencies in young patients suggests a need for alternative approaches to assessing value for money, where evidence is limited and there is potentially substantial benefit, although this is subject to further investigation. Where there is potential for a new treatment to be lifesaving, consideration could be given to interim funding arrangements, via managed access arrangements, while additional data are generated for use in a subsequent cost-effectiveness review. Further research is needed to identify the most appropriate mechanism for providing timely access to potentially one-time, curative therapies at value for money.

Chapter 3: A PSM to assess the impact of an OBA on cost-effectiveness of CAR-T

Gye A, Goodall S, De Abreu Lourenco R. Cost-effectiveness Analysis of Tisagenlecleucel Versus Blinatumomab in Children and Young Adults with Acute Lymphoblastic Leukaemia: Partitioned Survival Model to Assess the Impact of an Outcome-Based Payment Arrangement. Pharmacoeconomics. 2023 Feb;41(2):175-186. doi:10.1007/s40273-022-01188-w

Abstract

Objective: This research assesses the impact of an OBA linking CR to survival as a means of maintaining cost-effectiveness for a CAR-T in young patients with ALL.

Methods: A PSM was used to model the cost-effectiveness of tisagenlecleucel versus blinatumomab in ALL from the Australian healthcare system perspective. A decision tree modelled different OBAs by funnelling patients into a series of PSMs based on response. Outcomes were informed by individual patient data, while costs followed Australian treatment practices. Costs and QALYs were combined to calculate an ICER, reported in USD (2022) at a discount rate of 5% on costs and outcomes.

Results: For the base case, incremental costs and benefit were $379,595 and 4.27 QALYs, giving an ICER of $88,979. The ICER was most sensitive to discount rate ($57,660 - $75,081), "cure point" ($62,718 - $116,206) and extrapolation method ($76,018 - $94,049). OBAs had a modest effect on the ICER when response rates varied. A responder-only payment was the most effective arrangement for maintaining the ICER ($88,249 - $89,434) although this option was associated with the greatest financial uncertainty. A split payment arrangement (payment on infusion followed by payment on response) reduced variability in the ICER ($82,650 - $99,154) compared with a single, upfront payment ($77,599 - $107,273).

Conclusion: OBAs had a modest impact on reducing cost-effectiveness uncertainty. The value of OBAs should be weighed against the additional resources needed to administer such arrangements, and importantly overall cost to government.

Highlights

- HTAs of CAR-Ts have been associated with a high uncertainty. OBAs aim to address uncertainty associated with the translation of trial outcomes to longer-term clinical outcomes. The extent to which OBAs alleviate uncertainty over the longer term is largely unknown.
- There was a modest impact on reducing cost-effectiveness uncertainty under each OBA scenario compared with other sources of uncertainty in the model, whereas the potential financial impact uncertainty of an OBA was high. This emphasises the need for careful consideration in making recommendations for OBAs, particularly given the resources and complexities associated with real-world data collection and payment arrangements.
- If the main concern of governments and payors is the financial impact of high-cost therapies, then cost containment measures such as financial caps or price-volume agreements may be a more efficient approach to managing the high financial burden associated with cell and gene therapies compared with OBAs.

Introduction

CAR-T therapies were the first cell and gene therapies to undergo HTA globally. At the time of assessment, clinical evidence was from single-arm studies and data on their long-term benefits and safety were immature[42, 43, 116, 117]. Evidence limitations, together with the high cost of a once off treatment meant that HTA agencies grappled with a high level of decision uncertainty[116, 117, 119]. Consequently, public funding for CAR-T was often conditional on MAPs[120].

MAPs have been proposed as potential solutions for addressing uncertainty where there is high clinical need but limited clinical evidence together with high upfront costs and consequently elevated financial risk[1, 37, 40, 121-125]. A key recommendation from the NICE assessment of methods of review, economic evaluation and appraisal of cell and gene therapies was the importance of innovative payment methodologies for technologies where there is both a high level of uncertainty

and high expected patient benefits[114]. OBAs are a way of addressing clinical uncertainties and financial risk associated with cell and gene therapies [37, 40, 53-57], although their ability to address uncertainty in cost-effectiveness has not been assessed. OBAs link the net price of a medical technology to clinically relevant endpoints at the patient level[39, 53, 121, 125, 126] (the taxonomy of OBAs in relation to MAPs has been described extensively[121, 122, 125]).

A review of HTAs of CAR-Ts globally showed substantial variation in modelled, long-term benefit, particularly in young patients[120]. This variation was attributed to limited clinical evidence and the application of different extrapolation approaches beyond the observed period in the trials[120]. OBAs are tasked with addressing uncertainty over the longer-term. But the extent to which this occurs in practice, either for cost-effectiveness or total financial exposure, remains largely unknown. The main objective if this research was to assess the value of OBAs in dealing with uncertainty in cost-effectiveness by linking CR to survival in young patients with ALL treated with tisagenlecleucel. This will assist in determining whether decisions to publicly fund cell and gene therapies should be conditional on OBAs. CR was the outcome of interest because it is a short-term objective outcome, allowing an OBA to be enacted over a reasonable timeframe, and CR has been linked to improved survival[127]. The impact of the timing of outcomes assessment and distribution of payments on cost-effectiveness was also assessed.

Methods

Study setting and patient population

Australia was the setting for the economic analysis from a healthcare system perspective. The population was children and young adults (3 – 23 years of age) with relapsed or refractory ALL, based on evidence for tisagenlecleucel was from two phase II, single-arm, multicentre studies, ELIANA[23] and ENSIGN[128] .

Intervention and comparator

The CAR-T of interest was tisagenlecleucel. The intervention pathway commenced with the intention to treat with tisagenlecleucel, from the point of leukapheresis, followed by lymphodepleting chemotherapy before receiving a single infusion of tisagenlecleucel[33]. In accordance with the clinical trials, a small proportion of patients did not proceed to infusion due to an AE disease progression or death [23]. The comparator was blinatumomab, the standard of care in Australia prior to tisagenlecleucel being available and as accepted by MSAC in its consideration of tisagenlecleucel[14]. Blinatumomab is administered as a continuous infusion over a 28-day treatment cycle, and patients receive up to 5 cycles of treatment[129]. Evidence for blinatumomab was from a single-arm phase I/II study in young patients with relapsed/refractory ALL[85]. Another immunotherapy, inotuzumab ozogamicin is also funded in Australia for ALL, for use after blinatumomab, although was not considered a relevant comparator because it is not registered for use in children (<18 years)[130].

Model structure

The model contained treatment specific structures. For tisagenlecleucel, a PSM was preceded by a decision tree to model the pathway from leukapheresis to assessment of response, similar to previous approaches[131-133] (Figure 6). Patients infused with tisagenlecleucel were assessed for response at 3 or 12 months (reflecting possible OBA approaches).

Response was defined as a CR or CR with incomplete blood count (CRi), consistent with the primary outcome of the tisagenlecleucel clinical studies[23, 84]. Patients who did not achieve a CR/CRi or were lost to follow-up were considered non-responders. Because tisagenlecleucel may be used as a bridge to allogeneic SCT, responders were separated according to whether they received subsequent SCT or no SCT. SCT was considered separately in the model due to its high cost and the uncertainty around the proportion of patients who will receive an SCT following tisagenlecleucel. Patients who died before a response assessment were assigned costs and outcomes for the preceding time-period. Patients unable to receive an infusion due to an AE or disease progression

proceeded to treatment with the comparator and were assigned the same costs and outcomes as blinatumomab in addition to associated pre-infusion costs for tisagenlecleucel.

Following the decision tree, patients moved to a PSM corresponding to the outcome achieved at the assessment point; response (no SCT), response (with SCT) or no-response. Patients who achieved a response could either remain progression-free, progress or die, with the proportion of progression-free patients derived directly from the EFS curve, the proportion dead as 1 minus the OS curve, and the proportion progressed as the difference between the OS and EFS curves [64]. It was assumed that non-responders had progressive disease (PD), and therefore could only progress or die. The results for the progression-free survival (PFS), progressive disease (PD) or dead in each sub-group were combined to calculate the total costs and benefits of the entire cohort.

Treatment initiation with blinatumomab was considered from the point of infusion, hence the entire patient cohort was modelled using a single PSM consisting of 3 health states; PFS, PD and dead, without considering response status (as there is no known OBA associated with public funding for blinatumomab on the PBS). A one-month cycle length with half-cycle correction was applied and costs and benefits were measured over a lifetime horizon due to the potential curative benefit of tisagenlecleucel. Costs and outcomes were discounted at a rate of 5%, as recommended by MSAC Guidelines[30] (Table 5).

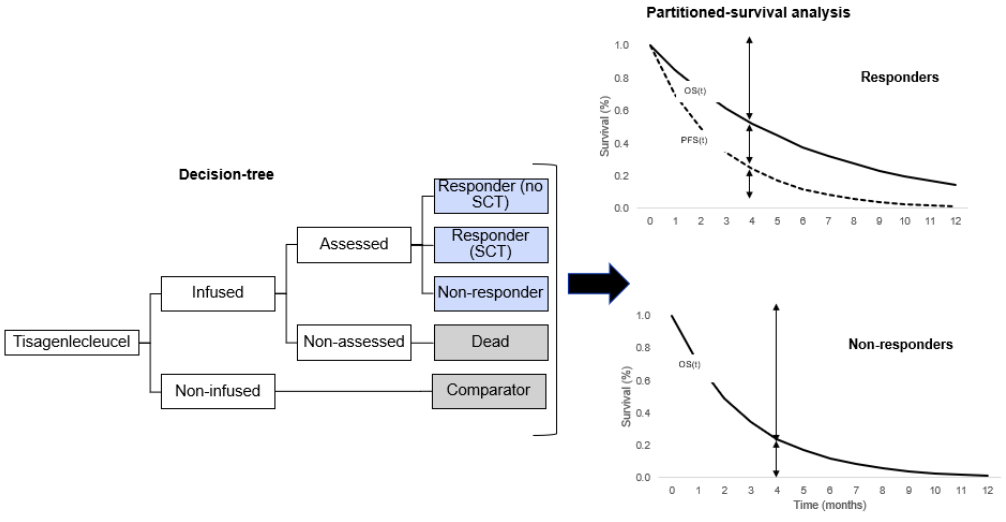


Figure 6 Decision-tree and partitioned survival model structure

OS indicates overall survival; PFS, progression-free survival; SCT, stem cell transplant; t, time.

Outcome measures

Modelled benefits were measured in LYs and QALYs derived from OS and EFS. EFS was measured from the time of first tisagenlecleucel infusion to relapse, death due to any cause or treatment failure, and considered representative of the PFS health state. OS was measured from the time of first tisagenlecleucel infusion to the time of death due to any cause. For blinatumomab, OS was measured from the start of treatment until death or date of last evaluation for all treated patients. EFS was not reported in the blinatumomab clinical study[85]. EFS for blinatumomab was estimated assuming a constant cumulative HR of 0.83 between OS and EFS over time, based on the relationship observed between OS and EFS Kaplan-Meier (KM) curves from a published study of mitoxantrone in paediatric ALL[127]. The impact of this assumption was tested in sensitivity analyses using the lower and upper range of hazard ratios (HRs) for EFS: OS from the mitoxantrone study[127] (Table 5).

Data analysis

Following visual inspection of the KM curves for OS for the ELIANA and ENSIGN studies and testing for statistical significance (HR 0.62, 95% confidence interval [CI]: 0.36 – 1.0; *P* = 0.098; Supplementary Figure 17, Appendix 1), the data from the studies were pooled. OS was grouped according to response status; non-responders were patients not in CR/CRi at the specified timepoint and included patients who had never achieved a CR/CRi or had achieved a CR/CRi prior to the specified timepoint but had subsequently relapsed (Figure 7A). The EFS) analysis only included patients who achieved a CR/CRi at the specified time point (Figure 7B).

The approach to the sub-group analysis by response for EFS followed the same approach to that described for OS. Analyses used data censored for SCT to allow for sensitivity analysis on different rates of subsequent SCT post infusion with tisagenlecleucel. Data for patients who received SCT following infusion with tisagenlecleucel were not analysed separately due to small patient numbers, and SCT censored data were applied to this patient group.

A 30-day window either side of each response time point was included to reflect the variability in timing of response assessments in clinical practice. In the studies, clinical assessments were conducted monthly for the first 6 months, consequently at the 3-month time point (61–122-day period) there was potential for duplicate patient entries as patients could have been assessed up to 3 times. To eliminate duplicate patient entries, only the last assessment during the 61 – 122-day period was included. A summary of the number of patients in each sub-group and by time point relative to the overall cohort is presented in Supplementary Table 13, Appendix 1).

For blinatumomab, time-to-event data were reconstructed from the published KM OS curve[85] using the software DigitizeIt. Pseudo-patient level data were generated using the approach by Guyot et al. 2012[134] and KM analysis performed following the methods described by Wei and Royston 2017[135]. The statistical software packages R[44], RStudio[136] and STATA[137] were used for the analysis of individual patient data (IPD) and generating KM data.

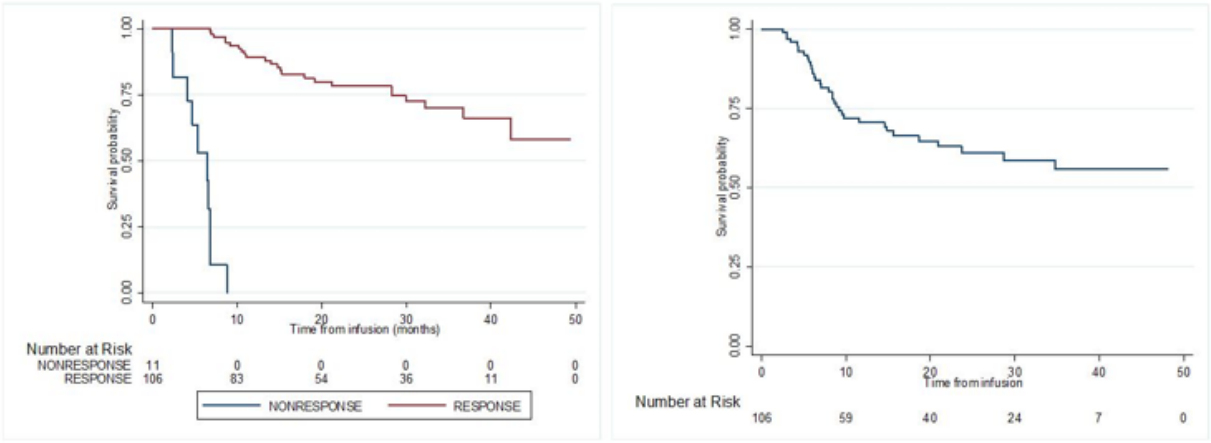


Figure 7 Kaplan-Meier analysis of tisagenlecleucel for (A) overall survival by responders and non-responders and (B) event-free survival for responders

Extrapolation of time-to-event data

In selecting the most appropriate approach to extrapolating survival data, duration of patient follow-up, completeness of the data, and level of censoring of the observed data was taken into account[64]. HTA agencies generally recommend the use of parametric models over Cox

proportional hazard regression models where data are immature[64, 138]. Additionally, because the model used sub-group data for tisagenlecleucel, an assumption of proportional hazards for the overall population was not appropriate. Instead, independent parametric models were fitted to each patient group in the model and the survival estimates weighted by the proportion of patients in each group (Supplementary Figure 19, Appendix 1). Although not used in the extrapolation, the HR and confidence interval (CI) for OS of tisagenlecleucel versus blinatumomab was derived using a Cox proportional hazard regression model, showing a significant improvement in OS for tisagenlecleucel for the overall cohort (Supplementary Text, Appendix 1).

Selection of the 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[139] (Table 5). Extrapolations were applied from the point on the KM curve where patient numbers were small (<12 patients) due to a high level of censoring[28] (Table 5). EFS curves were constrained by the OS curve, so that EFS did not exceed OS at any time point. For blinatumomab, the extrapolated EFS curve was based on the HR of EFS: OS as described above.

Long-term survival

Extrapolation of the observed data using parametric models continued until year 5 ("cure point") after which a standardised mortality ratio (SMR) was applied to age-adjusted all-cause mortality from Australian life tables[140]. An SMR of 9.05 was used based on a Canadian cohort study in childhood cancer patients who had survived at least 5 years[141]. SMR adjusted all-cause mortality was applied to both OS and EFS from year 5 onwards based on the observed relationship between OS and EFS[136], leading to a convergence of EFS and OS over time.

Utility values

Utility values for the PD and PFS health states of the model were calculated from patient-level EQ-5D data from the ELIANA study using UK preference weights[142] and applied to both arms of

the model due to the absence of published EQ-5D data for blinatumomab. Additionally, a general disutility associated with serious adverse events (SAEs), sourced from an economic analysis in chronic lymphocytic leukaemia[143], was applied to each arm weighted by the duration and frequency of SAEs from the clinical studies[23, 85] with the exception of grade 3/4 CRS, where a higher disutility was assumed due to its potentially high severity. An additional disutility was also applied to the proportion of patients who went on to receive an SCT assuming a duration of disutility of 1 year[144]. The utility and disutility values are summarised in Table 5, with further information on the calculation of the disutilities (Supplementary Table 14, Appendix 1).

Resource use and costs

Cost inputs sourced from prior publications were adjusted for inflation using the Reserve Bank of Australia's (RBA) inflation calculator[145], and when sourced from international publications, converted to Australian dollars using RBA exchange rates on 4 April 2022[146]. For the purposes of publication, costs are reported in US dollars[146].

The base case assumed a single upfront payment of $375,000 for tisagenlecleucel based on the NICE published price[42]. The cost of blinatumomab was calculated from the Australian PBS price[147] using an average number of treatment cycles from the clinical study[85] noting that the net price may be lower due to confidential pricing arrangements (Table 5; Supplementary Table 16, Appendix 1). Ancillary costs associated with the administration of each treatment included costs of infusion, length of hospital stay and management of SAEs including use of tocilizumab for CRS and IVIg for B-cell aplasia (Supplementary Table 15 and Table 17, Appendix 1). For tisagenlecleucel, administrative costs included leukapheresis and bridging chemotherapy (Supplementary Table 15, Appendix 1). Subsequent SCT costs for tisagenlecleucel and blinatumomab were estimated from a local costing study[148]. Ancillary costs were calculated by multiplying the percentage utilisation of each ancillary service from ELIANA[23] by the cost for each service estimated from Australian-relevant cost data (Supplementary Table 15 and Table 17, Appendix 1). Other disease management costs associated with PFSand PD were applied using an average cost from a cost-effectiveness analysis for

pixantrone in adult non-Hodgkin lymphoma[149]. Resource use and costs for tisagenlecleucel and blinatumomab are summarised in Supplementary Table 15 - Table 18, Appendix 1.

OBA scenario analyses

Two different response-based payment structures were considered: 1) split payment; payment 1 on infusion and payment 2 on response, or a smaller payment where patients could not be assessed for response (lost to follow-up), 2) single payment on response only. The amount per payment was weighted by the proportion of responders and non-responders to equal a weighted price of $375,000 for each scenario (Table 5). An equal weighted price was maintained across each OBA scenario because the purpose of the analysis was to test the impact of different payment structures, as opposed to the impact of a lower net price. To assess the impact of the OBA scenarios on the ICER, response rate was varied by ± 20% and rates of non-response, dead and lost-to-follow-up were varied proportionally (Table 5). Additionally, the differential cost of each scenario compared with the base case was calculated assuming a population size of 100 patients, to assess the budget impact of each payment structure.

Sensitivity analyses

Variables tested in sensitivity analyses were those that had previously been identified to have a substantial impact on cost-effectiveness of tisagenlecleucel in ALL[61, 120, 150]. These included discount rate, type of parametric extrapolation, long-term survival, SCT rate, infusion rate and IVIg use, as well as response rate (Table 5).

Table 5 Key parameter summary

Tisagenlecleucel	**Base**	**Sensitivity**	**Source**
Response rates[1]			
Response[2]	0.81	0.65, 0.97	ELIANA[23], ENSIGN[84]
No SCT	0.74	0.59, 0.89	
Subsequent SCT	0.07	0.06, 0.08	
Non-response	0.08	0.15, 0.01	
Dead	0.09	0.17, 0.01	

Lost to follow-up	0.02	0.04, 0.00	
Parametric extrapolation			
OS - Responders	Lognormal	Loglogistic, Gompertz	-
OS - Non-responders	Gompertz	-	-
EFS - Responders	Lognormal	Loglogistic, Gompertz	-
Extrapolation point (months)			
OS – Responders	40	20	-
OS - Non-responders[3]	6	-	-
EFS - Responders	40	20	-
Cure point, years	5	2,10	-
Long-term SMR	9.05	-	-
Tisagenlecleucel pricing[4]			
Base case[4]	$375,000	-	NICE[42]
Split[4]			
Payment 1 (infusion)	$206,271	-	-
Payment 2 (response)	$206,271	-	-
Payment 2 (lost to follow-up)	$82,508	-	-
Responder only[5]	$462,963	-	-
Resource use			
Proportion infused	0.83	0.66, 1.00	ELIANA[23], ENSIGN[84]
Proportion SCT[6]	0.09	0.27, 0.00	
IVIg use	0.88	0.70, 1.00	
IVIg duration, years	3	2.5, 80	
Blinatumomab			
SCT rate	0.34	-	Von Stackelberg[85]
OS parametric curve	Lognormal	-	-
OS extrapolation point (months)	25	13	-
HR EFS: OS	0.83	0.76, 0.99	-
Cost of blinatumomab	$49,127	-	PBS[147]
Utility and disutility values			
PFS	0.80	-	ELIANA[23]
PD	0.63	-	
Grade 3/4 CRS	-0.8	-	Assumption

Other SAEs	-0.1	-	Casado[143]
Subsequent SCT	-0.57	-	Sung[144]
Discount rate	5.0%	1.5%, 3.5%	MSAC[30]
SCT cost	$218,021	-	Gordon[148]

CRS, cytokine release syndrome; EFS indicates event-free survival; HR, hazard ratio; IVIg, intravenous immunoglobulin; PD, progressive disease; PFS, progression-free survival; SAE, serious adverse event; SCT, stem cell transplant; SMR, standardised mortality ratio; OS, overall survival.

[1]Infused population

[2]Defined as complete remission

[3]Extrapolation point not tested in sensitivity analysis due to short follow-up period due to low survival probability for non-responders.

[4]A published price for tisagenlecleucel was not available in Australia, therefore a price of 375,000 USD was assumed, based on the NICE published price[42]

[5]Weighted by the proportion of responders, non-responders and lost to follow-up at 3 months.

[6]As a proportion of the infused population

Results

Base case

Applying a single, upfront payment of $375,000 for tisagenlecleucel resulted in a total cost of $585,890, 7.13 LYs and 5.36 QALYs. The corresponding results for blinatumomab were costs of $206,294, 1.80 LYs and 1.09 QALYs. This gave an incremental cost of $379,595 and incremental benefit of 5.32 and 4.27 for LYs gained and QALYs gained, respectively. The ICER was $71,318 per LY gained and $88,979 per QALY gained over a patient's lifetime (Table 6). Results were very similar when assessed using the 12-month response rate for tisagenlecleucel; $90,129 per QALY gained over a patient's lifetime (Table 6). The 12-month analysis is not discussed further due to the similarity in results to those of the 3-month analysis.

Table 6 Base case results by timing of response assessment at 3 months and 12 months

	3 Months		**12 Months**	
	Tisagenlecleucel	**Blinatumomab**	**Tisagenlecleucel**	**Blinatumomab**
Outcomes (discounted)				
Discounted LYs	7.13	1.80	7.35	1.80
Discounted QALYs	5.36	1.09	5.53	1.09
Costs (discounted)				
Tisagenlecleucel[1]	$385,667	n/a	$385,668	n/a
Blinatumomab[1]	$24,710	$145,355	$24,710	$145,355
IVIg	$23,841	$4,382	$21,981	$4,382
PFS	$41,217	$7,128	$42,602	$7,128
PD	$97,787	$49,429	$100,229	$49,429
SCT[2]	$12,667	n/a	$31,636	n/a
Total discounted	$585,890	$206,294	$606,825	$206,294
Incremental				
Discounted costs	$379,595		$400,532	
Discounted LYs	5.32		5.55	
Discounted QALYs	4.27		4.44	
ICER				
Cost/LY	$71,318		$72,206	

Cost/QALY	$88,979	$90,129

N/a indicates not applicable; EFS, event-free survival; IVIg, intravenous immunoglobulin; LY, life year; PD, progressive disease; PFS, progression-free survival; QALY, quality adjusted life year; SCT, stem cell transplant.
[1]Includes ancillary costs
[2]Cost of SCT not considered separately in the blinatumomab arm of the model but was included in the total cost of blinatumomab.

OBA scenario analyses

A change of ± 20% in response rate had different impacts on the ICER depending on the type of payment structure applied (Figure 8 and Figure 9; Supplementary Table 19, Appendix 1). For the split payment scenario, the ICER range was $82,650 – $99,154 per QALY gained. There was only minor variation in the ICER for the responder only payment scenario, from $88,249 to $89,434 per QALY gained. For comparison, variation in the ICER was greatest with a single upfront payment (base case) ranging from $77,599 – $107,273 per QALY. The reverse effect was seen when the financial impact was calculated for each scenario; the greatest variability in differential lifetime financial cost was associated with a responder only payment (± $9,082,757), followed by a split payment arrangement (± 5,514,492) with the least variation (±$2,857,757) associated with the base case single upfront payment when response rate was varied ± 20% (Figure 9).

Sensitivity analyses

The ICER was most sensitive to discount rate, "cure point" and type of parametric extrapolation (Figure 8). A discount rate of 1.5% had the biggest impact on improving cost-effectiveness resulting in a decrease in the ICER to $57,660 per QALY. Conversely, extending the cure point to 10 years had the biggest impact on reducing cost-effectiveness by increasing the ICER to $116,206 per QALY. The type of parametric extrapolation also had a substantial impact on the ICER, varying from $76,018 per QALY with an exponential equation to $94,049 per QALY with Gompertz. An assumption of lifetime IVIg duration and an increase in SCTs post infusion with tisagenlecleucel increased the ICER considerably ($105,351 and $95,509 per QALY, respectively). Other variables tested in sensitivity analyses had a relatively minor impact.

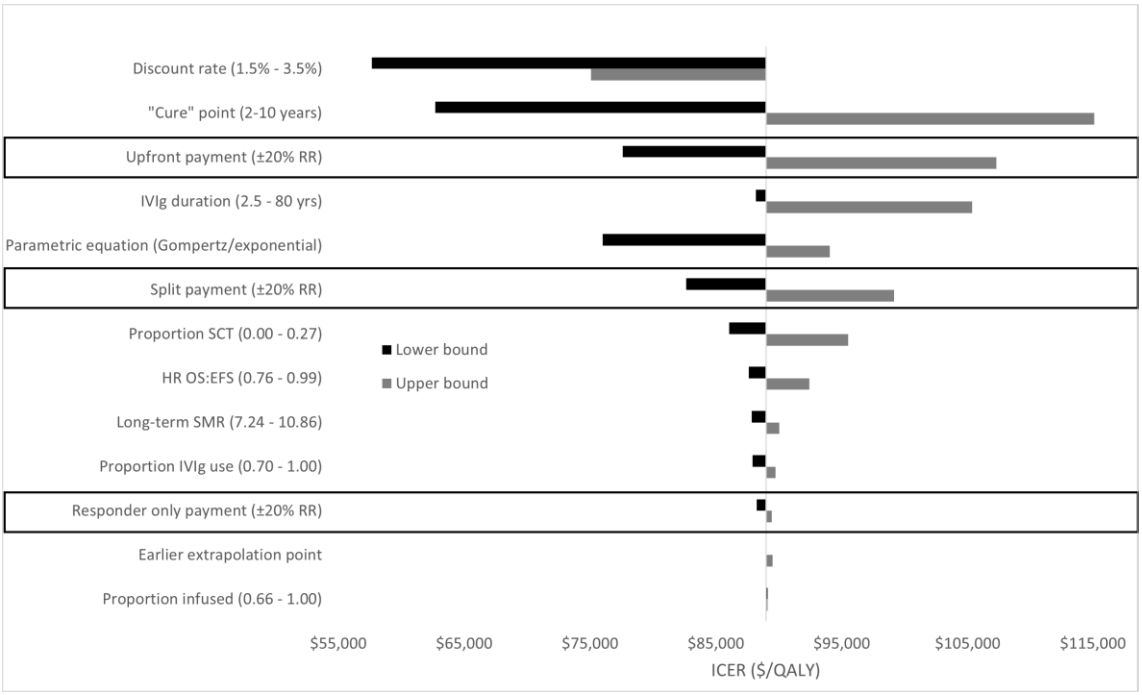


Figure 8 Tornado diagram of cost-effectiveness for OBA scenarios (boxed) compared with other sensitivity analyses

EFS indicates event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; OS, overall survival; QALY, quality adjusted life year; RR, response rate; SCT, stem cell transplant; SMR, standardized mortality ratio.

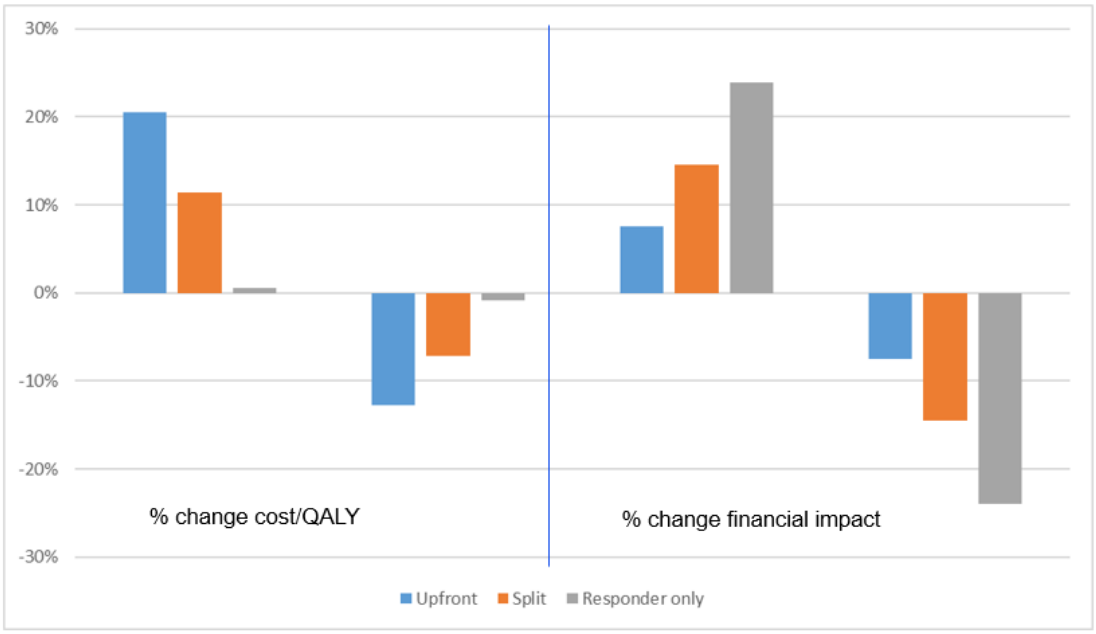


Figure 9 Change in financial impact and cost-effectiveness (incremental cost per QALY) under varying response rates for the base case and each OBA scenario

Note: Financial impact was calculated as the difference from base case in lifetime incremental cost of tisagenlecleucel versus blinatumomab for 100 patients.
Note: Adapted from original figure in publication to better convey the change in cost-effectiveness versus financial impact
RR indicates response rate; QALY, quality adjusted life-year.

Discussion

The base case ICER ($88,979 per QALY) was within the range of cost-effectiveness previously considered by MSAC in their original evaluation of tisagenlecleucel for ALL ($69,280 – $98,450 per QALY [AUD 92,373 – 131,267])[120]. Although the base case ICER was the same under each OBA scenario, each payment structure had a different impact on cost-effectiveness when response rates were varied, which is what the analysis sought to test. The responder-only payment was effective in maintaining a consistent ICER, although under a split payment arrangement the ICER changed by -7.1% - 11.4%. The biggest variation in the ICER occurred using a single upfront payment when response rates varied (-12.8% -20.6% change).

The responder only OBA was effective at maintaining a consistent ICER because under this arrangement the cost of tisagenlecleucel was directly linked to the benefit, so that when response rates altered, costs altered proportionately. Although intuitive, this requires a direct relationship between response and longer-term survival, which this analysis demonstrates. Furthermore, a responder only OBA resulted in high overall financial variability which may, in the eyes of the payor offset the benefit of a responder-only OBA in terms of maintaining cost-effectiveness.

Considering the high cost of cell and gene therapies, government may consider financial certainty more important than maintaining cost-effectiveness, particularly under a pay for responder arrangement which could see total financial costs increase substantially. Other considerations for a pay for responder arrangement include the reluctance of manufacturers to enter into an agreement where payment is entirely contingent on response and there is no recovery of costs for patients who do not respond.

In this analysis, the price per responder was determined by the proportion of patients in response in the clinical trials to give an overall weighted price of $375,000. This meant that for the responder-only OBA, there was no cost for patients who didn't achieve a response, but the cost was inflated for patients who responded (Table 5). Consequently, when response rates varied, cost-effectiveness, set at the response rate seen in the clinical trials, was maintained. This approach does

not adjust for a change in cost-effective price where response rates vary, highlighting the importance in setting the weighted price at the point of the initial cost-effectiveness assessment.

Not surprisingly, cure point was also a key driver of cost-effectiveness, as this determines the point at which the extrapolation of the survival curve is informed by disease-adjusted general population mortality. Interestingly, cure point and the type of parametric extrapolation were more important drivers of cost-effectiveness than response rate, highlighting the limitations of a surrogate outcome as the basis for an OBA.

The assessment of response to tisagenlecleucel at different time points had little impact on cost-effectiveness. Incremental costs, QALYs and the resulting ICERs were similar regardless of whether patients were assessed for response at 3- or 12-months post infusion. Patients who were assessed at 3 months experienced higher rates of progression and mortality compared with patients who remained in response at 12 months, although this was offset by improved survival for the non-responder group at 3-months compared with 12-months. Therefore, the timepoint for response assessment for an OBA may not be important, where the overall price is weighted by response rate.

To our knowledge, this is the first analysis to link response to survival to assess the impact of an OBA on both costs and benefits in an analysis of cost-effectiveness of tisagenlecleucel in ALL. The Institute of Clinical and Economic Review in their assessment of effectiveness and value of CAR-T therapies considered an option for an OBA, which was replicated in subsequent publications, although was only considered in relation to the distribution of payments and did not link response status to survival[131-133]. Other studies have looked at the impact on the cost-effectiveness of tisagenlecleucel of a response-only payment using clinical remission, although none accounted for any associated change in benefit[9, 61, 150-152].

A recent review of OBAs highlighted an increase in their use in Australia, Italy, Sweden, the USA, noting that publicly available information was limited, and perhaps more importantly, that there was even less information on whether the objectives of these OBAs in terms of realising value for money, had been achieved[59].

Accelerated registration pathways have created a dilemma for HTA agencies that rely on value- based assessments for public funding decisions, as conditional registrations do not require the level of evidence preferred by HTA agencies.[121] Arguably, this has led to an increased interest in OBAs. If OBAs are to be used as a tool for addressing uncertainty in HTA, then their utility in addressing clinical and economic uncertainty should be weighed against the costs and resources required to administer an OBA at the point of assessment of cost-effectiveness, and importantly their financial impact. Although the administrative costs of OBAs were not explored as part of this research, previous studies have highlighted substantial costs associated with their implementation[153, 154]. Decision makers may wish to consider alternative mechanisms of dealing with cost-effectiveness uncertainty, such as adopting conservative modelling assumptions, a higher cost-effectiveness threshold or lower levels of discounting. Cost containment could be achieved through financial caps or price-volume agreements that are easier to administer and do not rely on the collection of outcomes data.

Limitations

A limitation of the analysis was the small patient numbers by sub-group of the tisagenlecleucel data which may reduce the reliability of extrapolation of the data beyond the observed period. Analysis of the data by sub-group required access to individual patient data which means that application of this approach is likely to be limited to sponsor-led analyses. An inherent limitation was the lack of long-term, comparative data, although the included studies were considered the best sources of evidence by HTA agencies[120]. Although the analysis was limited by the level of evidence available, this is the issue that we sought to address and is one faced by decision makers on a daily basis.

Conclusion

In this analysis, a pay for responder arrangement was effective at maintaining a consistent ICER, although overall financial uncertainty was high. Compared with other variables in the model, a

split-payment OBA had a modest impact on reducing uncertainty in cost-effectiveness. Although the greatest variability in cost-effectiveness was seen with a conventional single, upfront payment, this also resulted in the least financial variability. This analysis used a weighted pricing approach so that the overall price for each OBA was equivalent to the base case single, upfront price at the response rates seen in the clinical trials. However, price is not readjusted for cost-effectiveness at different response rates, highlighting the importance in determining the weighted price at the point of initial cost-effectiveness assessment. Further work could consider measuring the impact of OBAs retrospectively to evaluate whether objectives were met.

Chapter 4: A DES model to incorporate CAR-T infusion wait-time

Gye A, Goodall S, De Abreu Lourenco R,. (in press) Discrete Event Simulation to Incorporate Infusion Wait-Time when Assessing Cost-effectiveness of a Chimeric-antigen Receptor T-cell Therapy. Value in Health.

Abstract

Objective: The main objective was to use DES to model the impact of wait-time, defined as the time between leukapheresis and CAR-T infusion, when assessing the cost-effectiveness of tisagenlecleucel in young patients with relapsed/refractory acute lymphoblastic leukaemia.

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 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 due to 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.

Conclusion: 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. DES is an important tool for economic modelling 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.

Highlights

- The main advantage of using discrete event simulation to model the cost-effectiveness of CAR-T was the ability to capture the manufacturing time, from the point of leukapheresis to CAR-T infusion.
- In modelling this process, we have shown that extended wait-time substantially reduces both the benefit and cost of CAR-T due to fewer patients proceeding to infusion.
- The model highlights the importance of capturing wait-time in an economic evaluation as it has implications for how arrangements between manufacturers and payors could be structured to deliver faster access to CAR-T for patients.

Introduction

The pathway for administration of 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[20]. The extracted T-cells are frozen and transported to a manufacturing facility for genetic modification to express chimeric antigen receptors that recognise antigen present on cancer cells[21]. 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 (r/r) ALL, the median manufacturing time for CAR-T cells was 1.48 months (range, 0.99 to 3.45)[23].

Strict regulatory standards for processing gene-modified cellular products have encouraged companies to adopt a centralised model for manufacturing, creating an access barrier as cells must be transported to these sites[71, 155] . 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[71]. There is also the risk of manufacturing failure due to poor quality or low volume of T-cells[156]. Young ALL patients who have failed multiple treatment options have a very poor prognosis[85], consequently an increase in CAR-T wait-time may result in disease progression, adverse events or patients succumbing to their disease.

Additionally, higher tumour burden has been associated with worse CAR-T outcomes in young patients with ALL[157,158]. 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 HTA agencies used decision-tree structures followed by PSM to capture the impact on costs and benefits of patients not proceeding to infusion[132, 159]. While this may be an appropriate modelling technique to ensure infused and non-infused 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 personalised medicines has been highlighted previously; waiting periods may impact outcomes, especially in conditions with high short-term morbidity and mortality[160].

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[69, 161-163]. 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[70, 162]. In healthcare research, DES has frequently been applied to modelling healthcare systems where capacity constraints need to be explicitly considered or modelling of disease progression where subsequent treatments impact costs and outcomes[164].

A previous study by Tully and colleagues[165] used DES to model the impact of CAR-T wait-time on 1-year mortality in adults with r/r 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 zero to between 1 - 9 months corresponded to an increase in the relative mortality rate of 6% - 125% over the same time[165]. 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 QALY. 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 MSAC at an ICER range of ($69,280–$98,450 per QALY [92,373–131,267 Australian dollars])[120]. 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, multicentre studies, ELIANA[23] and ENSIGN[84], 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 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 stabilise tumour burden[166, 167]. The comparator was blinatumomab, considered the standard of care prior to the availability of tisagenlecleucel by MSAC in Australia[14], as well as the main comparator for the economic modelling by the UK's NICE[42]. Blinatumomab is administered on an inpatient basis over a 28-day treatment cycle, and patients receive up to 5 cycles of treatment[129]. Data for blinatumomab were sourced from a published single-arm phase I/II study in young patients with r/r ALL[85].

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[168, 169].

Patients eligible for tisagenlecleucel entered the model at the point of leukapheresis. Following 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 and was therefore incrporated as a chance node based on the probability of manufacturing failure from ELIANA[23] (Figure 10 and Supplementary Figure 21, Appendix 2). If manufacturing was not successful, patients re-entered the model, providing another opportunity to proceed to successful infusion. This was considered to reflect clinical practice where manufacturing may be repeated. Given 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 re-enter the model in sensitivity analysis.

The model was structured to accommodate an OBA, based on patients achieving a CR at 3 months, following the approach applied in a previous model for tisagenlecleucel in r/r ALL[159]. Responders moved to the progression-free survival (PFS) health state, with the option to receive subsequent SCT, where they remained until they experienced a progression event or death. Non-responders moved to a progressive disease (PD) health state where 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[140] adjusted by a 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[141]. Previous economic evaluations for tisagenlecleucel in ALL considered by HTA agencies have applied cure-points between 2 – 5 years[120].

SMR adjusted general population mortality data was linked to individual patient age using bootstrapping. A uniform distribution was applied to the individual data for age from the clinical trials, and each data point assigned to the corresponding SMR adjusted mortality probability from Australian life tables. 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[85], 34% of patients proceeded to SCT and these patients are included in the OS data, consequently the benefit of patients proceeding to SCT is captured for blinatumomab.

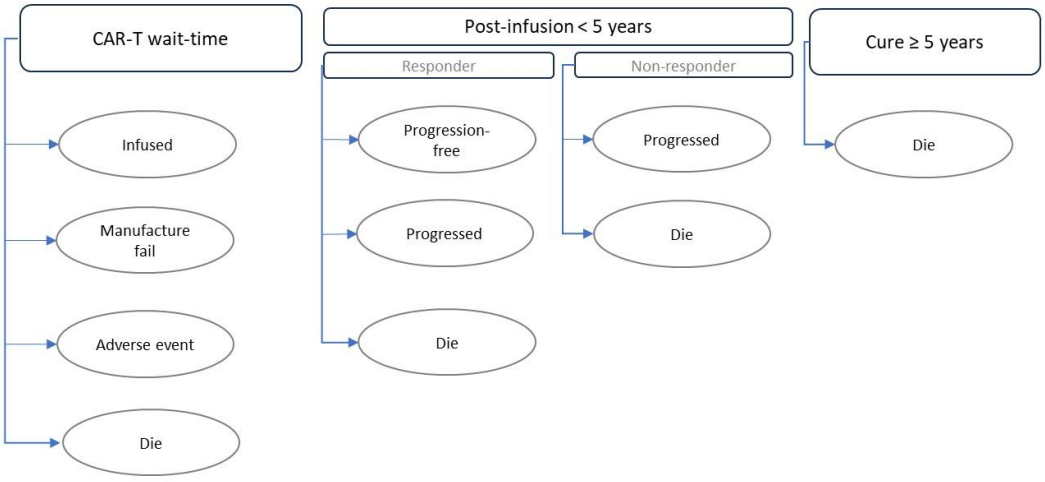


Figure 10 Discrete event simulation model structure for patients entering the tisagenlecleucel arm from the point of leukapheresis to assessment of response

Time-to-event distributions

Pre-infusion distributions

Data for the ELIANA and ENSIGN studies were pooled to derive time-to-event distributions, supported by visual inspection of the OS KM curves and no statistically significant difference in OS between the studies (HR 0.62, 95% CI: 0.36 – 1.0; P = 0.098). 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 months (Supplementary Figure 22, Appendix 2).

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[170], reconstructed

from the published KM OS curve following the approach by Guyot et al. 2012[134] and implemented using the statistical software R *IPDfromKM* package version 0.1.10[171]. The "curative intent" treatment group from this study was selected as 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 due to an AE. Patients not proceeding to CAR-T due to 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 parameter was calculated[172] 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 EFS and OS time-to-event data (Figure 11). 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 CR at 3 months. Time in PD was estimated from the OS data for non-responders 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[140]. 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 Supplementary Text, Appendix 2.

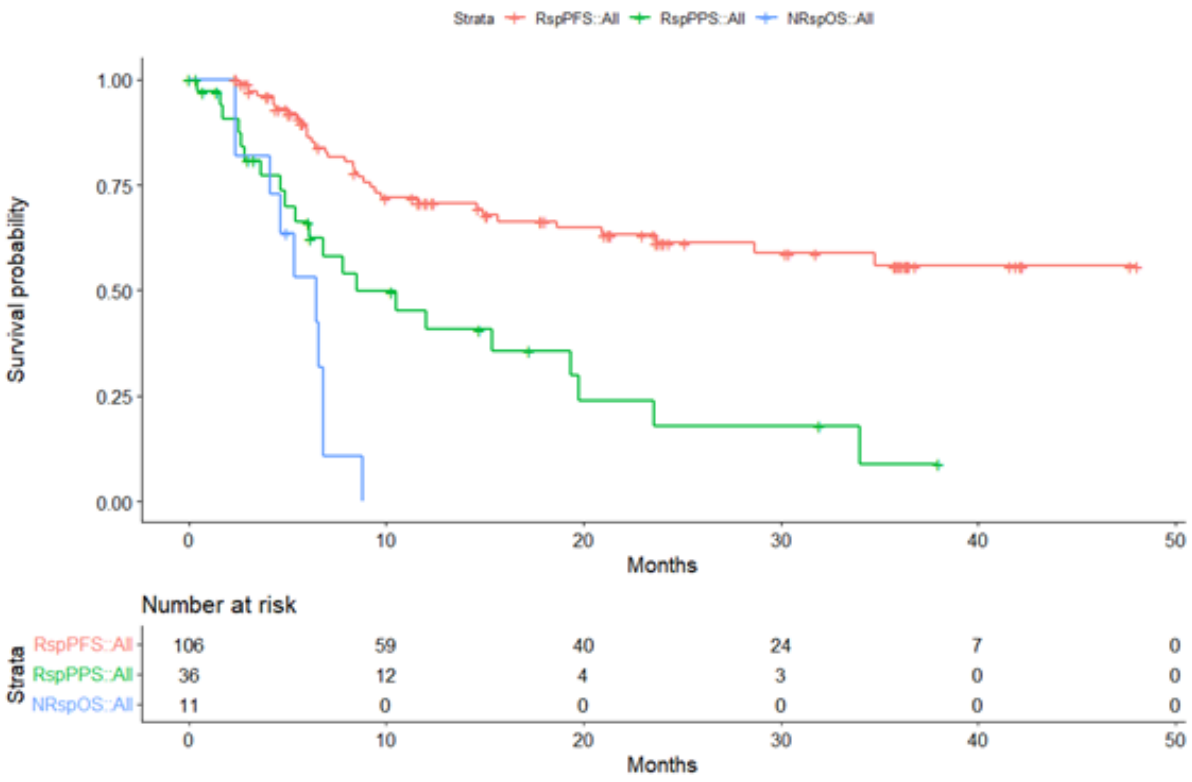


Figure 11 Kaplan-Meier survival curves for responder progression-free survival (RspPFS), responder progressive disease (RspPPS) and non-responder overall survival (NRspOS)

Blinatumomab

For blinatumomab, time in PFS was estimated by reconstructing individual data from the published KM OS curve[85], 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 paediatric ALL[127]. This assumption was tested in a previous economic evaluation by varying the HR between 0.76 – 0.99 and had minimal impact on the results[159]. Time-to-event data for blinatumomab patients moving from PFS to PD was not available, therefore the distribution for non-responders to tisagenlecleucel was applied.

The software R, Statistical Computing 2021 with the flexsurvreg package version 2.2[173] 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 AIC and BIC and whether the distribution was clinically and biologically plausible[139] (Supplementary Figure 24 and Figure 25, Appendix 2). The selected distributions are described in Table 7.

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[38] for patients aged 13 years and above. An implicit assumption is that EQ-5D data for patients above 13 years was applicable to those under 12 years and under. The PD state included EQ-5D assessments prior to infusion of tisagenlecleucel and after a PFS event, combined into a single PD utility value (Supplementary Table 21, Appendix 2). Utility data for patients prior to 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-time disutility was applied to each treatment arm to capture the loss of quality of life due to severe AEs including grade 3/4 CRS, other SAEs and subsequent SCT[39, 40]. Utilities used in the model are summarised in Table 7.

Costs

Costs were estimated from an Australian healthcare system perspective, consistent with MSAC Guidelines[30]. Cost inputs sourced from prior publications were adjusted for inflation using the RBA's inflation calculator[145], and when sourced from international publications, converted to Australian dollars using RBA exchange rates[146]. For the purposes of publication, costs are reported in US dollars using RBA exchange rates on 4 April 2022[50]. The cost for tisagenlecleucel was applied post-successful infusion in the base-case at a cost of USD 375,000 based on the NICE published price[42] as the Australian price was not publicly available. The cost per course of blinatumomab was calculated using the Australian PBS price[147] as USD 49,127 (AUD 65,502) and a mean number of treatment cycles from the clinical study[85], noting that the net price may be lower due to confidential pricing arrangements. Costs associated with the administration of each treatment were also included. Other costs included subsequent SCT[148], management of SAEs including use of tocilizumab for CRS and 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[159].

Model simulation

Long-term modelled benefits were measured in terms of 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 due to processing time. Costs and outcomes were discounted at a rate of 5%, as recommended by MSAC Guidelines[30]. 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[120], noting that Australia has no explicit

ICER threshold for cost-effectiveness and that the recommendation was conditional on a risk-share arrangement[28, 30].

CAR-T wait-time

Real-world data from the Centre for International Blood and Marrow Transplant Research (CIBMTR) 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[174]. We tested the impact of CAR-T wait-time on cost-effectiveness by multiplying the wait-time distribution by a factor of 0 – 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 impacted 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, as these were identified as key sources of uncertainty in HTA reviews[120]. Discount rate was tested because of the potential impact discount rate can have on a therapy with a single, upfront cost and potential lifetime benefit[1]. The model was structured to incorporate an OBA, allowing for the impact of different payment structures to be tested by varying response rates (further described in Supplementary Text, Appendix 2). 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 re-enter the model following manufacture failure.

Table 7 Key base case and sensitivity input parameters

Tisagenlecleucel			
Pre-infusion distributions	***Selected***	***Parameters***	***Source***
CAR-T wait-time	Lognormal	μ= 0.338 σ = 0.373	Pooled ELIANA[23] & ENSIGN[84]
Pre-infusion AEs[1]	Exponential	λ = 0.021	ELIANA[23]
Pre-infusion OS	Lognormal	μ= 1.611 σ = 0.828	Von Stackelberg[170]
Post-infusion distributions	***Selected***	***Parameters***	***Source***
Responder PFS	Lognormal	μ= 3.594 σ = 1.431	Pooled ELIANA[23] & ENSIGN[84]
Responder PD	Exponential	λ = 0.063	
Non-responder PD	Gompertz	λ = 0.536 γ = 0.018	
Pre-infusion probabilities[1]	***Base***	***Sensitivity (range)***	***Source***
Manufacturing failure[2] Adverse event Death	0.08 0.03 0.08	0, 0.1 - -	ELIANA[23]
Response probabilities[3]	***Base***	***Sensitivity (range)***	***Source***
Responders Subsequent SCT[4,5] Non-response Dead Lost to follow-up	0.81 0.22 0.08 0.09 0.02	0.65, 0.97 0, 0.30 Correlated Correlated Correlated	Pooled ELIANA[23] & ENSIGN[84]
Other important parameters	***Base***	***Sensitivity (range)***	***Source***
Mean CAR-T wait-time, months	1.55	0.00, 6.20	Pooled ELIANA[23] & ENSIGN[84]
"Cure point", years[6]	5	2, 10	MacArthur[141]
Long-term SMR	9.05	-	
CAR-T cost on infusion[7]	$375,000	-	NICE[42]
CAR-T cost on leukapheresis	-	$375,000	
Blinatumomab			

Distributions	***Selected***	***Parameters***	***Source***
OS	Lognormal	μ= 1.78 σ = 1.308	Von Stackelberg[85]
Other parameters	Base	Sensitivity (range)	Source
HR PFS: OS	0.83	-	Parker[127]
Cost	$49,127	-	PBS[147]
Tisagenlecleucel and blinatumomab			
Utility and disutility values[8]	***Base***	***Sensitivity (range)***	***Source***
Pre-infusion PD	0.65	-	ELIANA[23]
PFS	0.81	0.74, 0.88	
PD	0.69	0.60, 0.78	
Grade 3/4 CRS	-0.8	-	Assumption
Other SAEs	-0.1	-	Casado[143]
Subsequent SCT	-0.57	-	Sung[144]
Other parameters	Base	Sensitivity (range)	Source
Discount rate, %	5.0	1.5	MSAC[30]
SCT cost	$218,021	-	Gordon[148]

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

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

[2]An upper limit of 0.1 was appliedfor manufacturing failure because the probability of manufacturing failure was not expected to substantially increase from the clinical trials, due to an anticipated improvement in manufacturing procedures over time as processes are optimised[175].

[3]As a proportion of the infused population from ELIANA

[4]The proportion of patients who had undergone SCT at 12-months as a proportion of responders.

[5]Rate of subsequent SCT based on RWD was 22%, therefore a rate beyond an upper value of 30% tested in sensitivity analyses was not considered plausible[176].

[6]"Cure-point" was assumed at 5 years whereby all-cause mortality was adjusted by an SMR of 9.05 based on MacArthur[141], a Canadian cohort study in childhood cancer patients who had survived at least 5 years.

[7]A published price for tisagenlecleucel was not available in Australia, therefore a price of 375,000 USD was used from the NICE published price.

[8]Quality of life data not captured in ENSIGN therefore ELIANA was used a single source for utility value.

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 8 and Supplementary Table 22, Appendix 2), 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 zero 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 (Table 8; Figure 12). The large reduction in QALYs at 6.2 months for CAR-T reflects the poor survival outcomes for patients treated with salvage chemotherapy (median OS of 4 months[170]; Supplementary Figure 23, Appendix 2).

Costs for tisagenlecleucel were also sensitive to wait-time, with zero wait-time resulting in an increase in the costs for tisagenlecleucel to $689,569, due to more patients proceeding to infusion, whereas an increase in wait-time had the reverse impact on costs, reducing costs for tisagenlecleucel to $294,478 due to fewer patients proceeding to infusion (Table 8).

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 (Table 8; Figure 12). 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.

Table 8 Costs, QALYs and ICERs for tisagenlecleucel versus blinatumomab at different wait-times, when CAR-T cost is applied post-infusion versus pre-infusion

	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 (base case)								
Post-infusion payment[1]	**$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

ICER indicates incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[1]Base-case analysis results

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 (Table 9; Figure 12).

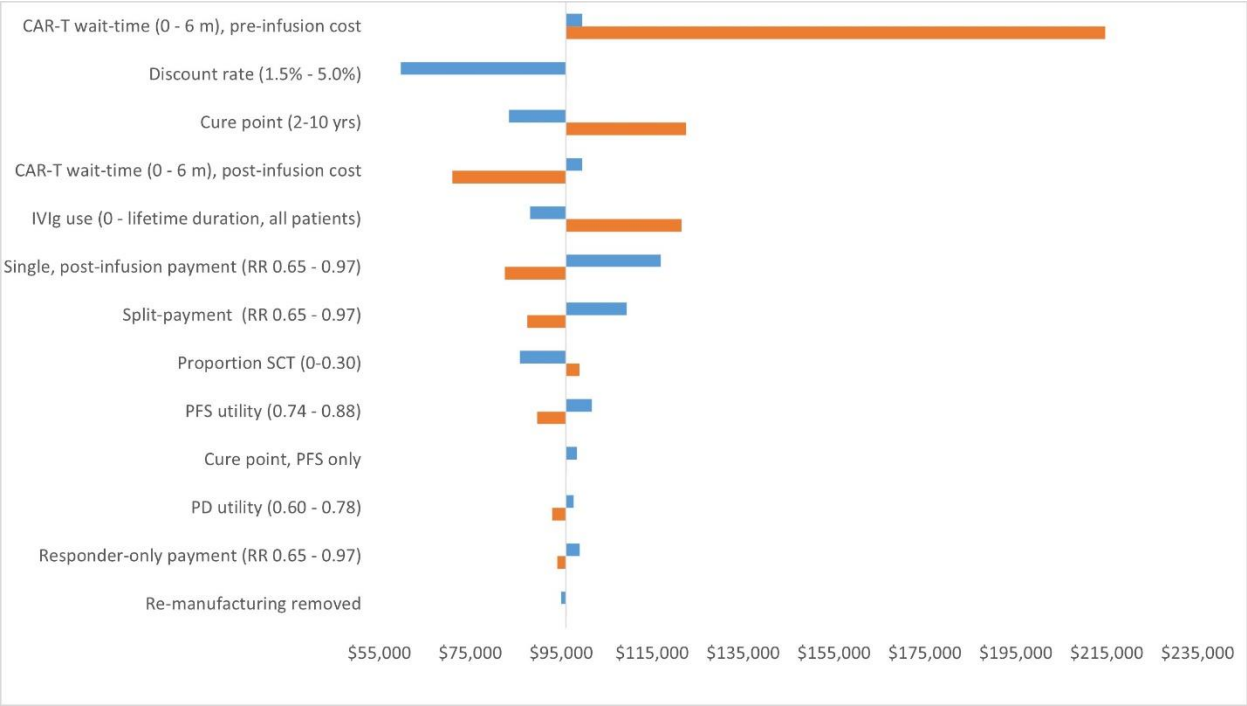


Figure 12 Tornado diagrams showing impact of parameters varied in sensitivity analyses on the incremental cost-effectiveness ratio

Note: 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

Table 9 Incremental costs, QALYs and ICERs for the sensitivity analyses

	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			
0.60	$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
RR 0.97	$539,894	5.73	$94,155
Re-manufacturing removed			

No model re-entry following manufacture fail	$397,918	4.19	$94,933

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

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 modelling 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 zero 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 polychemotherapies and SCT[170].

Despite the large QALY loss with increasing wait-time, the cost-effectiveness ratio fell due to 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, as the cost of infusion was incurred regardless of a successful infusion. A sensitivity analysis was conducted which 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 (as 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 timeframe, or perhaps a tiered payment arrangement, so that faster delivery times are associated with a higher payment. 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 modelling 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 two days, eliminating the need for T-cell activation or ex-vivo expansion[177], with a Phase I clinical trial underway in adults with B-cell malignancies[178]. Additionally, incorporating wait-time in an economic analysis may inform decisions on how access to current CAR-Ts is prioritised 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[165, 179]. 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 – 6 months compared with patients treated immediately[180]. In adult r/r DLBCL, an increase in wait-time from 1 – 9 months corresponded to an increase in mortality from 36.12% to 76.33%[165]. In another study, a reduction in CAR-T wait-time resulted in survival gains, with a mean of 0.27 - 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 due to lower tumour burden[179]. Another study used the relationship between lactate dehydrogenase (LDH) levels and tumour 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)[179]. We did not find an association between wait-time and OS post CAR-T infusion, therefore we did not adjust survival outcomes by wait-time in the model (Supplementary Text, Appendix 2).

We recognise the limitations of the model in terms of the non-comparative 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 sub-group 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 sub-group 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, due to 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.

Chapter 5: A comparison of PSM, STM and DES modelling techniques

Gye A, Goodall S, De Abreu Lourenco R,. (In Press) Different Models, Same Results: Considerations When Choosing Between Approaches to Model Cost-effectiveness of Chimeric-antigen Receptor T-cell Therapy. Pharmacoeconomics.

Abstract

Objective: CAR-Ts are 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 STM, PSM and DES.

Methods: Individual data for tisagenlecleucel for the treatment of young patients with ALL were used to populate the models. Costs and benefits were measured over a lifetime to generate a cost per 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 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-time and substantially reduce the benefit of CAR-T. This is an important consideration when selecting a model type for CAR-T, so that major drivers of uncertainty can be considered in funding decisions.

Highlights

- The unique characteristics of CAR-T warrant exploration of alternative modelling structures for assessing cost-effectiveness.
- The ability to incorporate an OBA and wait-time are important elements to consider when selecting a model for CAR-T
- All three model types incorporated an OBA, although changes in CAR-T wait-time were only tested using discrete event simulation (DES), due to the relative ease in in which more complex pathways could be modelled.

Introduction

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, 9]. Consequently, conventional modelling approaches may not be appropriate. Cost-effectiveness analyses of CAR-T considered by HTA agencies have relied on PSMs to inform public funding decisions[120]. PSM may be considered an appropriate choice over other approaches where time-to-event data are available, particularly OS and PFS, and is the approach most commonly applied in economic models assessing the cost-effectiveness of oncology medicines[65]. Within PSM, 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[63, 64]. 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[63, 64]. This led the NICE Decision Support Unit to recommend that PSMs should be accompanied by STMs to better assess the plausibility of extrapolations[64].

STMs include both cohort Markov models and individual patient models (known as microsimulation or Monte Carlo simulation)[67]. 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[64, 67]. Microsimulation STMs however require more computation time, a relevant consideration if probabilistic analysis is used[67]. STMs differ primarily from PSMs because the proportion of people moving between health states is determined using transition probabilities[63, 64, 67]. This means additional data are required over a conventional 3-health state PSM consisting of PFS, PD and death, to estimate the transition probabilities for patients in the PD state, not usually captured in analyses of clinical trial data[64].

To date, 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[70, 181]. 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[62, 69]. 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[182].

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 QALYs[182]. 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 ALL the median processing time for CAR-T cells was 1.48 months (range, 0.99 to 3.45) in the ELIANA trial[23], and is subject to variation in clinical practice[71, 155, 156].

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 OBA, and in the case of DES, factoring in CAR-T wait-time[159, 183]. In this paper we compare 3 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.

Methods

All models were designed to compare costs and benefits of CAR-T versus standard of care in a young population with r/r ALL. Benefits were measured in terms of cost per LY and QALYs from an Australian healthcare system perspective. Costs and benefits were discounted at a rate of 5% year, consistent with Australian Guidelines[29]. The methods reported here focus on the structure of the STM, as the PSM and DES models have been described in detail previously[159, 183], with the main parameter inputs summarised in Table 10 . The same assumptions and parameter inputs were applied consistently to enable comparison of the results across the model types. A detailed comparison of the model methods is provided in Supplementary Table 24, Appendix 3.

Table 10 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[23], ENSIGN[84]
Adverse event[1]	Exponential (λ = 0.021)	ELIANA[23]
Chemotherapy OS	Lognormal (μ= 1.611, σ = 0.828)	Von Stackelberg[170]
Pre-infusion probabilities[1]		
Death	0.08	
Adverse event	0.03	ELIANA[23]
Manufacturing failure	0.08	
Response probabilities[2]		
Responders	0.81	

Subsequent SCT[3]	0.22	
Non-responders	0.08	ELIANA[23], ENSIGN[84]
Dead	0.09	
Lost to follow-up	0.02	
Post-infusion distributions		
Responder PFS	Lognormal (μ= 3.594, σ = 1.431)	
Responder PD	Exponential (λ = 0.063)	ELIANA[23], ENSIGN[84]
Non-responder PD	Gompertz (λ = 0.536, γ = 0.018)	
Blinatumomab		
Survival distributions		
OS	Lognormal (μ= 1.78 , σ = 1.308)	Von Stackelberg[85]
PFS	HR adjusted OS	Parker[127]
Long-term extrapolation	SMR adjusted all-cause mortality at 5 years	MacArthur[141]
Costs		
Tisagenlecleucel (on infusion)[4]	$375,000	NICE[42]
Blinatumomab	$49,127	PBS[147]
SCT	$218,021	Gordon[148]
Utility and disutility values		
Pre-infusion PD	0.65	
PFS	0.81	ELIANA[23]
PD	0.69	Casado[143]
Grade ¾ CRS	-0.8	Sung[144]
Other SAEs	-0.1	
Subsequent SCT	-0.57	

CRS indicates 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.
[1] Sourced from ELIANA only due to differences in reporting of patient disposition of the enrolled set
[2]Infused population
[3]The proportion of responders who underwent SCT at the 12-month assessment point was applied in the model.
[4]A published price for tisagenlecleucel was not available in Australia, therefore a price of 375,000 USD was assumed, based on the NICE published price[42]

Clinical data

All models used data sourced from two single-arm clinical trials of the CAR-T therapy, tisagenlecleucel[23,128] in young patients (3 – 23 years of age) who had relapsed or were refractory to multiple lines of treatment, including possible allogeneic 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[85]. Access to the IPD from the clinical trials enabled sub-group analysis to be performed to generate KM survival data to inform the economic models. For blinatumomab, survival data were reconstructed from the published data[85]. Data analyses were performed using the software R, Statistical Computing 2021 and STATA 17, StataCorp 2021.

STM structure

The model was built in Microsoft Excel® using a monthly cycle length modelled over a lifetime horizon (Figure 13). The STM was structured to accommodate an OBA for tisagenlecleucel, using CR (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 4 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 3 health states, PFS, PD or Dead.

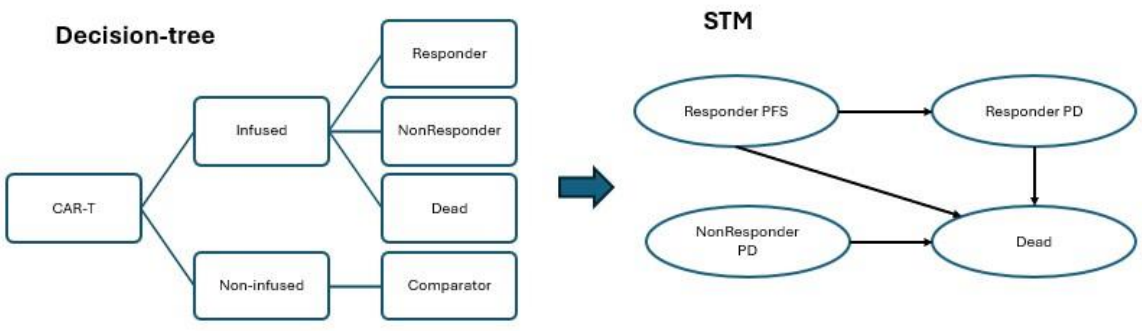


Figure 13 State transition model structure with preceding decision tree for the CAR-T arm

CAR-T indicates chimeric-antigen receptor T-cell therapy (CAR-T); PD, progressive disease PFS, progression-free survival; STM, state transition model

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 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:

$$\mathrm{RspPD} = [(S^{PFS}(t) - S^{PFS}(t+1)) \times S^{PD}(\mathrm{t})] \times \mathrm{P_{Rsp}}$$

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. PRsp 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 Rsp*PD* state, background mortality was applied using 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[70]. 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[85], adjusted by a constant cumulative HR of 0.83 between OS and PFS[159]. 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.

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 AIC and BIC and also whether the extrapolated portion was clinically and biologically plausible[139] . Extrapolations were applied from the point on the KM curve where patient numbers were small (<12 patients) due to a high level of censoring[28]. Long-term survival beyond 5 years "cure-point" was extrapolated using a general mortality probability derived from Australian life-tables , adjusted by applying a SMR of 9.05 from a Canadian cohort study in childhood cancer patients who had survived at least 5 years[141], to the proportion of patients remaining in *PFS* at 60 months. 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.

PSM 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 until year 5, after which SMR adjusted, all-cause mortality was applied. For the blinatumomab arm, a conventional 3-health state structure was applied with OS and PFS survival probabilities generated using the same approach as described from the STM.

DES structure

Unlike the STM and PSM models, the DES model was developed using specialised software (Treeage Pro 2022, Williamstown, MA) 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[168, 169]. 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 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 IPD 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.

Utilities

The same utilities were applied to each model, with the exception of DES that included a pre-infusion utility during the CAR-T wait-time period. Utility values were calculated from patient-level EQ-5D-3L data from the ELIANA study using UK preference weights[142]. The PD state included EQ-5D assessments prior to infusion of tisagenlecleucel (while patients are in a progressive state after prior treatment) and after a PFS event, combined into a single PD utility value. Utility data for patients prior to infusion with tisagenlecleucel was applied to the pre-infusion period in the DES model. For blinatumomab, no published utility data were available, therefore the tisagenlecleucel values were used. A one-time disutility was applied to each treatment arm to capture the loss of quality of life due to severe AEs including grade 3/4 CRS, other SAEs and subsequent SCT.

Costs

Cost inputs sourced from prior publications were adjusted for inflation using the RBS inflation calculator[28], and when sourced from international publications, converted to AUD using RBA exchange rates[29]. All estimates of costs were calculated in AUD using RBA exchange rates[146].All estimates of costs were calculated in AUD, although,costs were reported in USD[29] consistent with previous publications of the PSM and DES models[159, 184], using RBA exchange rates, April ***2022***[146].The base case assumed a single payment of $375,000 for tisagenlecleucel at the point of infusion, converted from the NICE published price[30] as the Australian price was 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 adverse events including tocilizumab for CRS and 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[31] as $49,127 (AUD 65,502) and an average number of treatment cycles from the clinical study21, 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.

Model assessment

A comparison of the models comprised a quantitative assessment, in terms of costs, QALYs and the ICER, and a checklist developed of the components captured by each model type, based on a set of parameters important in modelling the cost-effectiveness of CAR-T.

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[185, 186]. 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 CR 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[159].

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 (Table 12). 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.

Results

Quantitative performance

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 (Figure 14). 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 (Supplementary Figure 25, Appendix 3).

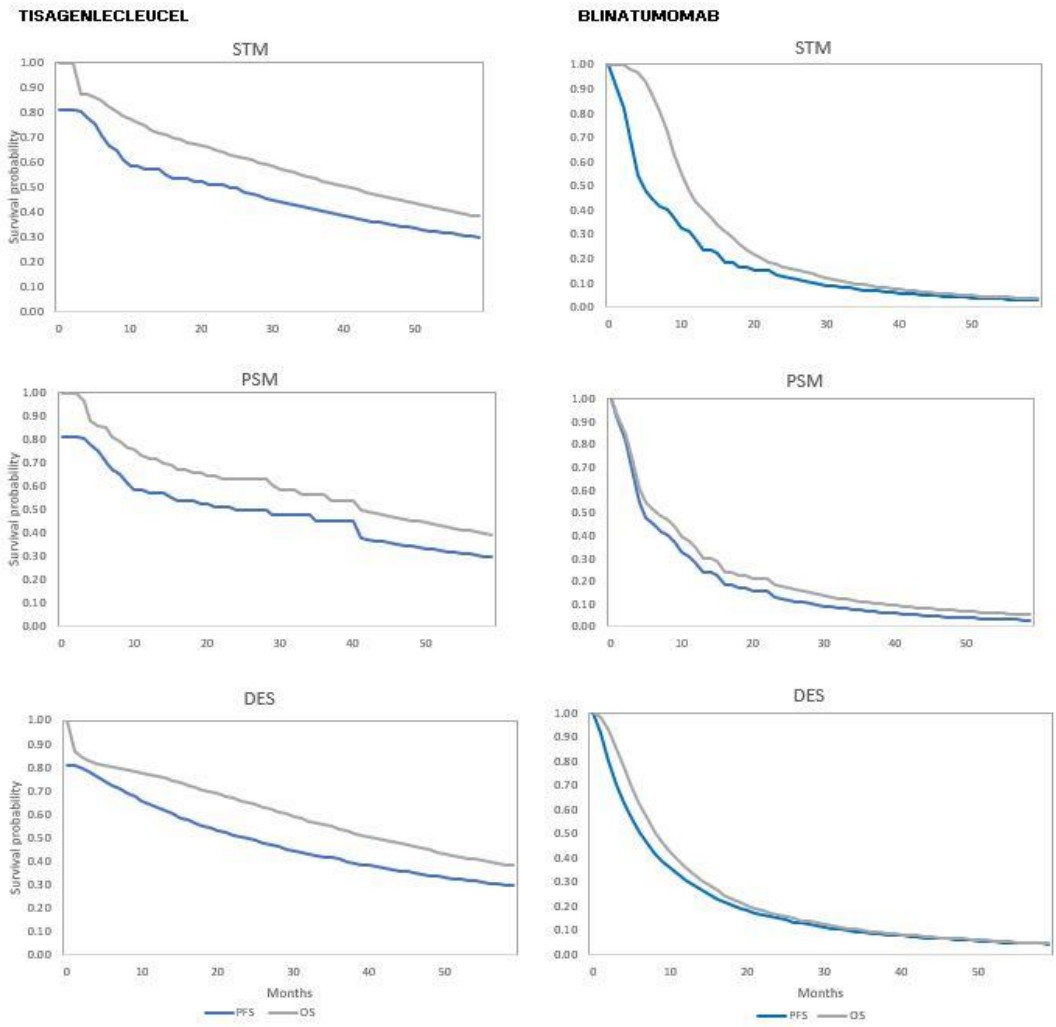


Figure 14 Health state occupancy for each model structure for tisagenlecleucel and blinatumomab

Base case results

The base case results by model type were relatively similar (Figure 15;

Table 11). 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.

Table 11 Base case results by model type

	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

DES indicates discrete event simulation; PSM, partitioned survival model; QALYs, quality adjusted life year; STM, state transition model

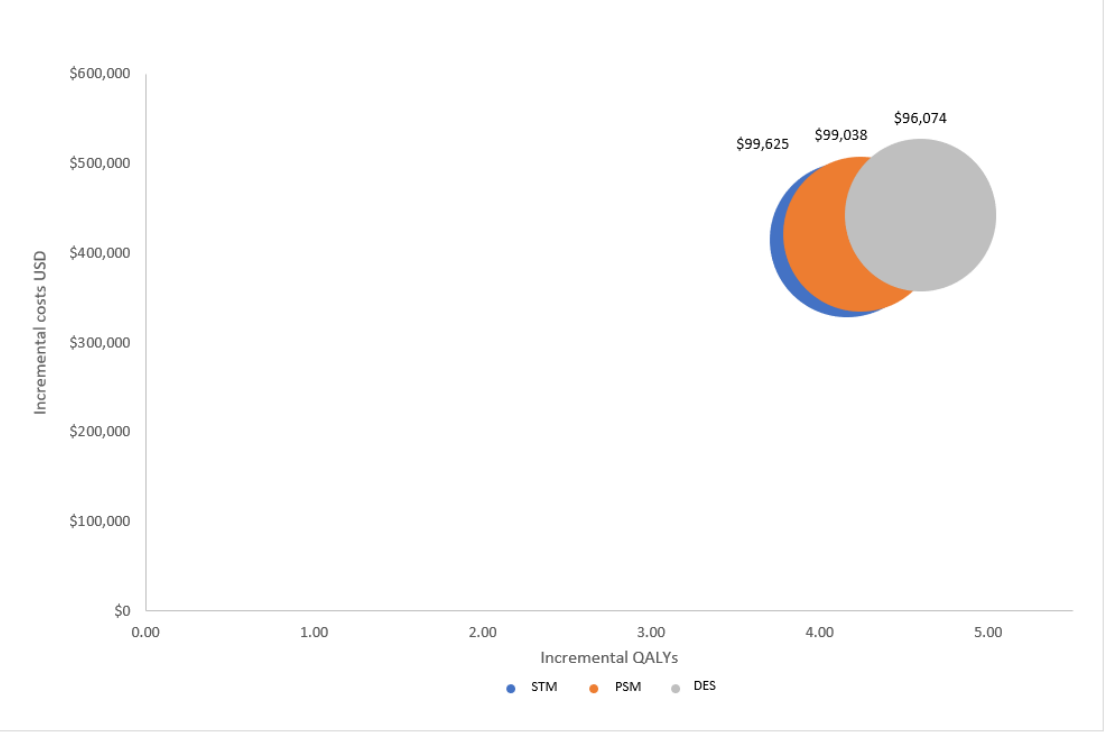


Figure 15 Bubble plot showing base case results for STM, PSM and DES models

DES indicates discrete event simulation; PSM, partitioned survival model; STM, state-transition-model.

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 (Figure 16; Supplementary Table 25, Appendix 3). 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.

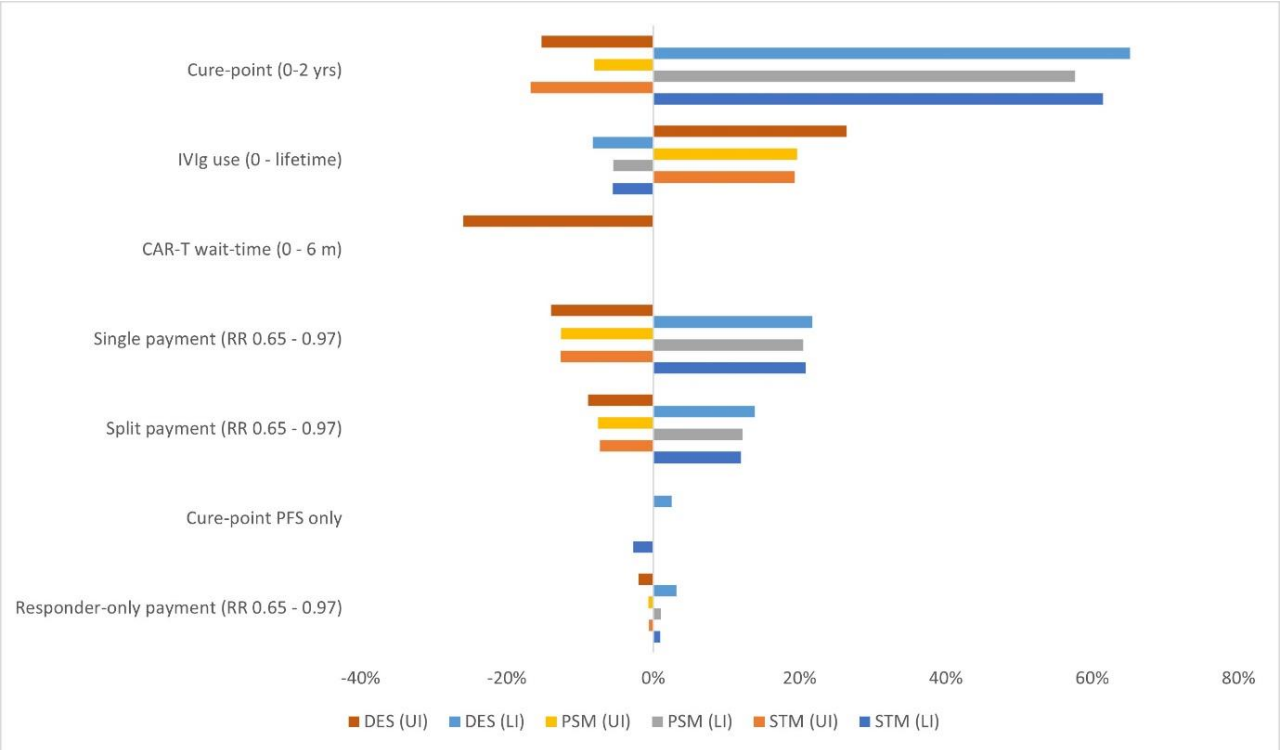


Figure 16 Sensitivity results: percentage change in the ICER from the base-case for each model type

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 indicates chimeric antigen-receptor T-cell therapy; m, months; IVIg, intravenous immunoglobulin; QALY, quality adjusted life year.

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 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 12).

Table 12 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.	✗	✗	✓
	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.	✓	✗	✓
Complexity	The model could be populated using the published data, without the requirement for additional analysis using IPD.	✗	✗	✗
Validity	The model generates similar results to alternative model types of the same therapy and patient population.	✓	✓	✓

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

Notes: ✓ indicates "yes", ✗ "no".

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, 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, is the potential for 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 impacting 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[159]. 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[186] applied PSM and STM approaches using data in late-stage cancer

patients. The PSM produced ICERs between £234,829 to £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[185] evaluated the impact of PSM and STM approaches on survival estimates of different therapies 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[185]. 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[168]. Similarly, Senanayake et al.[187] 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[188] 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 disadvantages of DES were the level of complexity in modelling complex systems, and skill needed to develop the model as well as the additional data requirements[188].

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 pathways by calculating the time to a competing event, without the need

for separate health states. However, it is recognised that this 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 theoretically 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[189, 190]. The 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[62].

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[62, 188]. 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[162]. We were able to link individual patient age it 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[68]. 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[68, 168].

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.

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[159, 184]) 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[191]. 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 a previous study by Cranmer and colleagues did not incorporate PSA when comparing results of PSM and STM approaches[186].

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 OBA and wait-time. Ultimately, determining the most appropriate model structure will require longer-term data to assess the true predictive value of each model.

Chapter 6: Discussion and conclusion

Summary

CAR-T provides patients with leukaemia and lymphoma an effective treatment option, where previously there were limited alternatives and survival outcomes were poor[23, 88]. At the same time, these novel therapies have been disruptive to health care systems, challenging public funding decisions regarding their value for reimbursement and overall cost to governments' healthcare budgets[11]. In conducting a review of HTA evaluations of CAR-T, this research identified key issues encountered by decision-makers, specifically, limited clinical evidence, high upfront cost, a complex manufacturing process and the potential for cure. While these challenges are not are not new to HTA, it is the combination of these elements that heighten the difficulty of assessing the opportunity cost of funding CAR-Ts.

OBAs have been widely used by HTA agencies in an attempt to alleviate the clinical uncertainties and financial risk of single-dose cell and gene therapy.[36, 39, 52-56.] However, the extent to which OBAs address clinical and economic uncertainty was not assessed in economic evaluations of CAR-T[120]. By structuring an economic model to incorprate different OBAs, this research demonstrated that the level of cost-effective uncertainty addressed by OBAs is relatively modest compared with other parameter assumptions, and are accompanied by high financial variability, highlighting the need for careful consideration of the financial implications of OBAs, and the potential to exceed anticipated budget impacts [159].

Additionally, manufacturing wait-time is an important parameter to consider in assessing the cost-effectiveness of CAR-T. Using DES to model the treatment pathway from the point of leukapheresis to infusion of CAR-T, this research shows that extended CAR-T wait-time has the potential to substantially reduce the benefit of CAR-T at the population level, and that tailored arrangements between manufacturers and payors are needed to ensure speed of access to CAR-T.

While a comparison of different modelling approaches - STM, PSM, DES - yielded similar base-case cost-effectiveness results, DES was more flexible in its ability to incorprate CAR-T wait-

time, and as such is an important tool for decision makers so that major drivers of uncertainty can be considered when making funding decisions for these therapies.

This work was not intended as an Australian case-study, but rather a case-study for cell and gene therapy using tisagenlecleucel for the treatment of ALL as an example. All economic models were considered from a healthcare system perspective, using Australian costs, where available, converted to USD, and UK preference weights to derive utility values. The objective was to explore the impact of different parameters and approaches, using different model structures, on cost-effectiveness of CAR-T. Therefore, the results reflect a modelling exercise to identify the key attributes of CAR-T that impact cost-effectiveness, fulfilling the objective of developing a model structure that can best accommodate these attributes, namely OBAs and wait-time.

HTA evaluations of CAR-Ts

The first phase of this research involved a systematic review of HTA evaluations of CAR-Ts to better understand the challenges faced by HTA agencies in assessing their cost-effectiveness. Economic modelling approaches, outcomes in terms of costs, LYs, QALYs and recommendations regarding cost-effectiveness were compared, focusing on differences, in terms of key clinical evidence, economic approach, and outcomes (costs, QALYs and ICERs), between young and older patients.

Despite the consistency in evidence and model structure, the incremental benefit of CAR-T for the same indication varied substantially between evaluations. This was particularly evident in the young population with ALL for which incremental QALYs ranged from 3.67 to 10.6, and ICERs ranged from $39,146 to $98,450 per QALY. In adult DLBCL incremental QALYs were more consistent across the models, although the ICER range was still wide ($57,046 – $268,415), largely driven by the differences between the models in incremental costs.

The large differences in modelled benefit were unexpected, given the clinical data to populate the models was sourced from the same studies. These differences were likely attributable

to the different extrapolation approaches as well as different discount rates depending on the standard rate of a particular country. While the differences in costs were not considered an unusual finding, as healthcare costs are expected to vary between countries, an understanding of how different assumptions on resource measurement, parameter inputs and modelling may be driving differences in costs is important, given their importance in determining the ICER. This was not explored further due to the limited data available on costs; often only aggregate information on cost was available, and there were inconsistencies in how costs were reported across the different economic evaluations.

In making their funding decisions, most HTA agencies applied conditional recommendations for CAR-T contingent on MAPs and, in the case of Australia there was a requirement for an OBA. While OBAs may have been a requirement in other countries, this information was not available publicly.

The impact of OBAs on cost-effectiveness uncertainty of CAR-T

Economic models identified in the systematic review of HTA evaluations of CAR-T therapies were not structured to assess the impact of an OBA in addressing cost-effectiveness uncertainty[120]. This prompted the second part of the research to assess the value of an OBA as a mechanism for managing long-term clinical and economic uncertainty, using tisagenlecleucel in ALL in the Australian setting as a case-study.

As part of this research 3 different types of payment arrangements were modelled:

1. Conventional upfront payment for all patients, with no recovery of costs when expected benefits are not realised in practice (risk weighted towards government).
2. Partial upfront payment followed by payment on a clinical outcome being achieved (split-payment OBA).
3. Delayed payment entirely contingent on an outcome being achieved (responder-only payment)

The first payment arrangement is the standard arrangement, whereby payment is received upfront once the patient receives the intervention. This was not considered an OBA, as payment is not linked to a clinically relevant outcome. The remaining two payment arrangements represent OBAs, as payment is linked to response, either as a split payment (partial payment on receipt of the intervention, and the remaining payment if response is achieved), or a response only payment, where payment is only made if the patient achieves a response. These two different types of OBAs were selected as they represent different levels of risk; the level of risk in a split-payment arrangement is weighted more towards the payer, and in a responder-only payment arrangement, the level of risk is weighted more towards the manufacturer.

OBAs were incorporated into using a decision tree to triage patients into a series of PSM structures dependent on whether the patient achieved a response (CR) at 3 months post-infusion with CAR-T. Using individual patient data to link response to OS and PFS, the impact of changes in

the proportion of patients in response at 3 months on cost-effectiveness was tested. Additionally, this research explored the impact of changing the payment structure of the OBA, using a split payment arrangement and a single payment on response only.

Each payment structure had a different impact on cost-effectiveness when the proportion of patients in response at 3 months, a key source of uncertainty, was varied. A split payment arrangement had a modest impact on the ICER of -7.1% to 11.4%, relative to the base case ICER, compared with a -12.8% to -20.6% change for a single payment on infusion, whereas a single payment on response was effective in maintaining a consistent ICER. By comparison, the ICER was more sensitive to discount rate, cure-point and type of parametric function used to model survival, consequently the level of uncertainty addressed by an OBA was relatively modest. In addition to cost-effectiveness uncertainty as affected by the response rate, OBAs had an impact on the overall financial cost of CAR-T, with a responder only payment resulting in high financial variability.

To our knowledge, this is the first analysis to empirically link response to survival in this indication to demonstrate the impact of a response-based OBA on cost-effectiveness. The benefit of incorporating an OBA into the model structures was the ability to test the impact of the OBAs relative to other model parameters, to determine the relative "value" of OBAs in their ability to address uncertainty in cost-effectiveness.

The impact of CAR-T infusion wait-time on cost-effectiveness

The next phase of this research applied DES as an alternative modelling approach to PSM to assess the value of CAR-T. DES was considered due to its ability to capture CAR-T wait-time, using an event-driven process to calculate the time to a competing event[69, 70].

The modelled results showed a change in CAR-T wait-time had a substantial impact on cost-effectiveness, attributed to the change in number of patients proceeding to infusion and therefore the overall cost and benefit derived from CAR-T at the population level. For the base-case analysis, mean CAR-T wait-time was 1.55 months, reflecting the mean wait-time from the ELIANA and ENSIGN trials, resulting in incremental QALYs gained of 4.60 and incremental costs of $441,652 giving an

ICER of $96,074 per QALY. When CAR-T wait-time was increased to 6.20 months, the model generated 2.78 incremental QALYs gained and incremental costs of $294,478, reducing the ICER to $71,112 per QALY. Conversely, when CAR-T wait-time was reduced to zero months the ICER increased to $99,602 per QALY because the increase in incremental QALYs to 6.30 was accompanied by an increased in incremental costs of $689,569.

The substantial impact of CAR-T wait-time on benefit to patients reflects the poor survival outcomes for children with ALL who have failed multiple treatment options and have a very poor prognosis[85]. In the model, an increase in CAR-T wait-time led to fewer patients proceeding to infusion due to death or disease progression, reducing the benefit of CAR-T but also the cost at the population level. Consequently, there was a decrease in the ICER with increasing wait-time. This inverse relationship between wait-time and the ICER was a function of the payment arrangement whereby the cost of CAR-T was only incurred once the patient was infused. In a sensitivity analysis, when payment for CAR-T was brought forward, to the point of leukapheresis, the ICER increased with an increase in CAR-T wait-time.

A comparison of modelling techniques

Considering the unique characteristics of CAR-T, another objective of this research was to explore alternative modelling techniques for assessing cost-effectiveness by applying STM, PSM and DES modelling techniques. Overall, the models generated similar results in terms of costs, QALYs and ICERs for the base-case and sensitivity analyses. While model structure did not meaningfully impact the results, there were advantages and disadvantages to each model in terms of their relative complexity, transparency, and flexibility. DES was the most flexible model in terms of incorporating CAR-T wait-time and different OBA structures, although was more data intensive, requiring additional analyses to model the competing risk of events during the pre-infusion phase, and additional sub-group analyses to derive the survival distribution for patients in PD. DES was less transparent, in terms of its operation, compared with STM and PSM approaches due to its computational method which required the use of specialised software. PSM was the simplest model

to implement primarily because it did not require additional sub-group analyses to model the survival of patients in PD, although was more rigid in its structure and less adaptable in terms of incorporating costs and benefits during the pre-infusion phase for CAR-T. Similar to DES, the STM approach required additional survival analyses for the sub-group of patients in PD, using transition probabilities to derive the proportion of patients moving from the PD to dead health states, as opposed to probability distributions to calculate the time to an event using DES.

Regardless of the type of approach, the modelled benefits and costs over a lifetime horizon were similar, as verified by a comparison of the model traces showing a similar proportion of patients in PFS, PD and dead health states over time, supporting the validity of the modelled results. When considering the modelled outcomes for the base-case analyses, a PSM structure was the simplest to implement and yielded similar results to the other more complex DES and STM structures. However, in terms of flexibility, DES was more amenable to capturing the pre-infusion phase to be able to test the impact of a change in CAR-T wait-time on population outcomes.

Application of this research to HTA

Since the appearance of cell and gene therapies on the horizon, HTA bodies have worked to identify whether changes are needed to current HTA processes to accommodate these new technologies. In 2017 Hettle and colleagues published a mock appraisal commissioned by NICE for a hypothetical CAR-T in paediatric ALL[9]. The authors concluded that existing HTA methods were sufficient to assess these types of therapies, noting that consideration should be given to investigating alternative payment arrangements to deal with the associated long-term uncertainty[9]. In 2019 the Institute for Clinical and Economic Review in the US undertook an assessment of its methods for evaluating treatments that represent one-time potential cures, based on their experience in evaluating the first CAR-T and gene therapies[78]. As a result, revisions were made to their value assessment framework, including cure-proportion modelling, standardised survival extrapolation methods, and perhaps controversially, the inclusion of additional elements of value

including the value of hope[78]. Following these initial reviews, cell and gene therapies have been assessed by different HTA bodies globally.

The research in this thesis identified substantial variability in the modelled lifetime benefit in young patients, highlighting a need to consider alternative mechanisms to manage long-term uncertainty[120]. More recently, Drummond and colleagues reviewed HTA reports for 9 different cell and gene therapies, identifying use of surrogate endpoints as the basis for registration, lack of a comparator arm, need for extrapolation of long-term endpoints and limited sample size as major issues in decision-making[11]. These issues are not new, and confirm the initial concerns raised in the literature regarding value assessment for CAR-T therapies[1, 11].

The literature continues to assert that ongoing data collection in the form of MAPs, including OBAs, is a solution to manage the long-term uncertainty and irrecoverable costs associated with a once only administration of therapies, like CAR-Ts[11]. However, major limitations with these types of arrangements remain, in particular the associated administrative challenges, patient and clinician follow-up, confounding of real-world data associated with subsequent therapies and lack of comparative data[11, 192].

The research in this thesis has identified several important methodological elements that should be considered in the HTA process for cell and gene therapies to ensure components contributing to their cost-effectiveness and financial impact are carefully assessed:

1. ***Economic models should be structured to incorporate OBAs***.

   This is important for several reasons:

   - To quantify the extent of cost-effectiveness uncertainty that can be addressed by an OBA, as well as the optimal structure in terms of the outcome selected for that OBA, and the frequency and timing of payments.
   - To quantify the level of financial uncertainty associated with an OBA in terms of the potential variability in overall cost to government/payors (which may be higher or lower than anticipated, depending on the outcomes generated in practice).

- To enable a review of the initial cost-effectiveness analysis, using the data generated from the OBA to understand the usefulness of the OBA in addressing cost-effectiveness uncertainty.

2. **Wait-time should be incorporated into the structure of an economic model for therapies with complex manufacturing processes, where there is potential for delay in treatment delivery**.
   - This research has demonstrated that delay in treatment delivery, particularly where survival outcomes are poor with current treatment options, has the potential to substantially reduce benefit due to fewer patients proceeding to treatment. It is therefore important to ensure that economic models are structured to capture wait-time, not only to ensure that estimates of cost-effectiveness capture all relevant effects, but also to inform how payment arrangements between manufacturers and payors/governments could be structured to ensure speed of access for patients.
   - Economic evaluations of cell and gene therapies should incorporate the treatment pathway starting at the point of leukapheresis rather than infusion given the importance of the time between leukapheresis and infusion on health outcomes and cost-effectiveness
3. **Selection of the type of model structure should be informed by the unique elements of the therapy that have potential impact on costs and benefits.**
   - Consideration should be given to using DES due to its flexible structure and amenability to capturing the unique elements of cell and gene therapies, in particular wait-time, outweighing the disadvantage of additional data requirements and reduced transparency compared with PSM and STM structures.

HTA bodies continue to review their methodological processes for assessing cost-effectiveness. NICE has recently undergone a review of their methods and processes for assessing new health technologies, making changes to the eligibility criteria for technologies considered as

HSTs, and more broadly, giving greater flexibility in terms of the type of evidence considered, particularly for rare diseases[193]. In Australia, an HTA review is currently underway and includes a review of HSTs encompassing cell and gene therapies[194]. It is anticipated that the findings and recommendations in this thesis will be valuable in contributing to the assessment of HTA methods to ensure timely and equitable access to cell and gene therapies.

Limitations

In developing the economic models, this research focused on a specific CAR-T, tisagenlecleucel, for ALL in young patients as a case-study and therefore may limit the applicability of these findings to other cell and gene therapies. Data used to inform the models relied on small patient numbers and comparisons by treatment arm were naïve in nature due to the absence of a comparative clinical trial for tisagenlecleucel. While this may reduce the reliability of the results, there was a high level of concordance in the cost-effectiveness results generated from three different model structures populated using different sub-group analyses of the data, suggesting that the methods used were reliable. Analysis of the tisagenlecleucel data required access to IPD which ensures robustness of the estimates but limits the replicability of the analyses presented. Additionally, application of the methods to other cell and gene therapies is likely to be limited to sponsor-led analyses where access to IPD is available. Estimating the curative potential of CAR-T was the main limitation of modelling its cost-effectiveness. The strength of the evidence to support assumptions of the long-term benefit of tisagenlecleucel was weak at the time of undertaking this research, available from two single-arm clinical trials with a follow-up period of approximately 5 years. Tisagenlecleucel was the first cell and gene therapy to be registered and reimbursed globally, with a novel mechanism of action involving the genetic modification of T-cells via a viral vector to bind to specific antigens on cancer cells. Although the biological mechanism of CAR-T suggests the potential to cure, no validated predictors of curative effective were available from the published literature, hence long-term extrapolation of the survival curves was based on data from a Canadian

cohort study in childhood cancer patients demonstrating that mortality risk was greatest for patients whose disease had reoccurred within 5 years of diagnosis[141]

In the STM and PSM models, parametric extrapolations were applied to estimate survival until year 5, after which an SMR, derived from the Canadian study, was applied to age-adjusted all-cause mortality from Australian life tables[137]. In the DES model, patients who remained alive at 5 years moved to a long-term survival health state where the same assumptions using SMR-adjusted time-varying probabilities derived from general population mortality were applied, consistent with the STM and PSM models. A "fully curative effect" (meaning long-term survival equivalent to the general population, without SMR adjustment) was not considered plausible given the immaturity of the tisagenlecleucel data. Although a "fully curative" effect wasn´t specifically considered the cure-point was brought forward to 2 years in a sensitivity analysis, leading to a substantial increase in QALYs. Previous economic evaluations for tisagenlecleucel in ALL considered by HTA agencies applied cure-points between 2 – 5 years[120].

The application of long-term survival using data from childhood cancer patients may under- or overestimate the benefit of CAR-T and that of the comparator, however this was identified as the best source of evidence on longer term survival available at the time. Over time, it is anticipated that assumptions of long-term survival with CAR-T will become more robust with the availability of mature data, and the potential for additional evidence generated from real world data (RWD)."Overall, the models were limited in terms of the non-comparative nature of the clinical evidence and limited patient follow-up in the context of a potentially curative therapy., however this was the issue that we sought to address and is one faced by HTA decision makers daily.

Areas for further work

Many of the solutions proposed to deal with the cost-effectiveness uncertainty of cell and gene therapies in the form of MAPs, and more specifically OBAs, have not been reviewed post-implementation, likely due to the confidential nature of such arrangements and lack of access to the data collected. However, further research is needed to determine the extent to which such arrangements alleviate cost-effectiveness uncertainty, and understand how OBAs should be structured, in terms of payment frequency, outcomes collected and duration of their implementation. Additionally, transparency in terms of the availability of information pertaining to OBAs to facilitate their review is needed.

Existing efforts in post-market, RWD collection via registries will address some of these challenges. For example, the CIBMTR registry in the US, originally established as a registry to collect outcomes on hematopoietic cell transplantation (HCT), now also serves as a registry for CAR-T therapies with a standardised approach for data collection, and data are used to assess outcomes in the real world setting[176]. Mandatory data collection, evidence generation and periodic review of MAP arrangements can be used to incentivise manufacturers to report data using established international registries. Governments, payors, and industry will need to work together to develop coordinated registries to collect data on real-world outcomes and costs, for both CAR-T and comparator treatments, to determine incremental costs and benefits in clinical practice.

Alternative mechanisms proposed in evaluating the cost-effectiveness of one-time therapies such as cell and gene therapies include the Institute for Clinical Review´s proposed 50%/50% shared savings model and a 150,000 USD cost-offset cap. In the 50%/50% shared savings model, only 50% of the cost-savings generated by the new treatment are assigned to the intervention arm of the model, alternatively, he 150,000 USD cost-offset cap involves capping the cost-offsets generated by the new treatment at 150,000 USD[131]. These approaches are intended to address the uncertainties in the long-term benefits of these therapies and the estimated cost-offsets to the healthcare system. Such novel approaches warrant further exploration in economic analyses of cell and gene therapies.

One of the key attributes of CAR-T is the potential for cure, which is the main driver of uncertainty in assessing it´s cost-effectiveness. Outcome-based MAPs have the potential to address uncertainties associated with clinical benefit, by linking payment to an outcome realised in practice. Therefore, the focus of this work was on outcome-based MAPs, and exploration of the literature was targeted towards use of outcome-based MAPs, as opposed to all financial mechanisms available to payers. A summary of the studies identified in the published literature is included in Appendix 4, Table 26. Further work could explore more broadly the types of financial mechanisms available to payers for managing financial and clinical uncertainty associated with cell and gene therapies.

Conclusion

Ascertaining a high level of certainty in determining a cost-effective price for a one-time cell and gene therapy requires generating long-term, comparative data to assess incremental costs and benefits over a patient's lifetime. Under these circumstances, it is important to develop an economic modelling approach that can best address uncertainties with the data available at the initial point of assessment for reimbursement. This research has demonstrated the importance of designing flexible model structures to incorporate OBAs to determine an appropriate payment structure, outcome selection, and contractual conditions for implementation. This research has also shown the importance of considering the unique attributes of cell and gene therapies in economic model design, specifically in the case of CAR-T where extended wait-time substantially reduced the benefit of CAR-T at the population level. While it is important to look back to assess how OBAs have performed so far, consideration also needs to be given to a bespoke structure to model the unique elements of CAR-T, to assist in alleviating uncertainty, easing the burden on decision makers at the initial point of assessment to facilitate speed of access to patients.

Appendix 1

Supplementary Text

A Cox proportional hazards regression model to estimate the HR and its CI for OS of tisagenlecleucel versus blinatumomab (Figure 17). The rate of death (hazard) for blinatumomab was 3.4 times the hazard for tisagenlecleucel (HR 3.43, 95% CI: 2.26 – 5.19) and this was statistically significant ($P < 0.001$). Graphs of the scaled Schoenfeld residuals and log of the negative log of survival versus the log of time shows the proportional hazards assumption is met because they appear to be parallel residuals (Figure 18).

Supplementary Figures

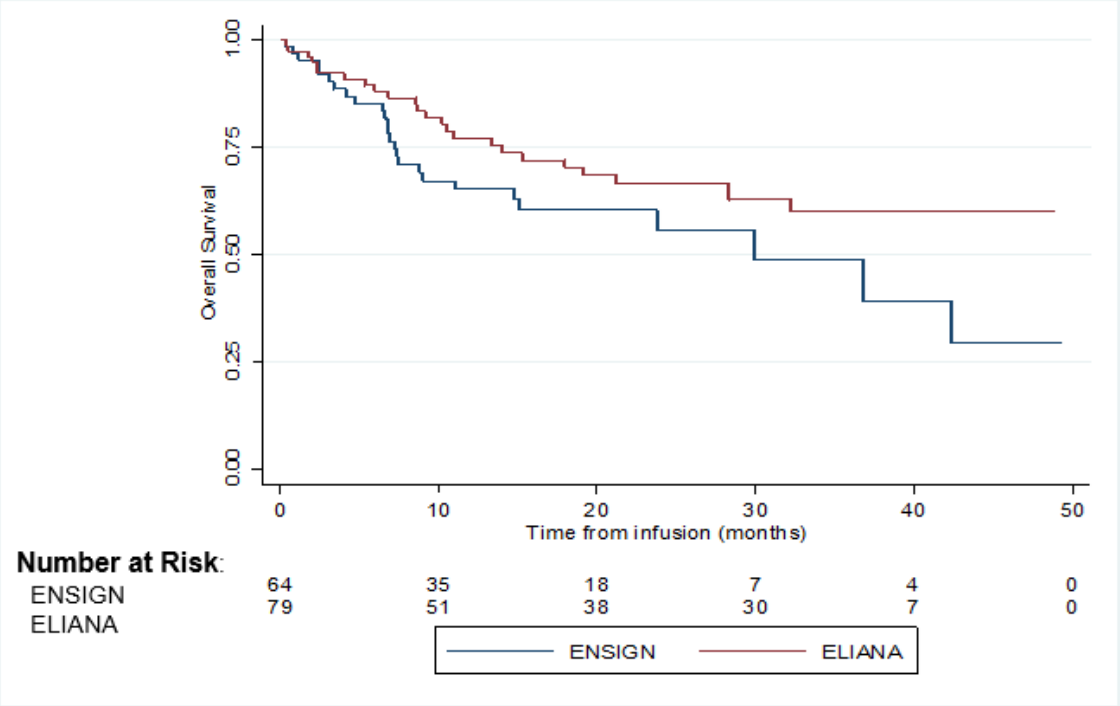
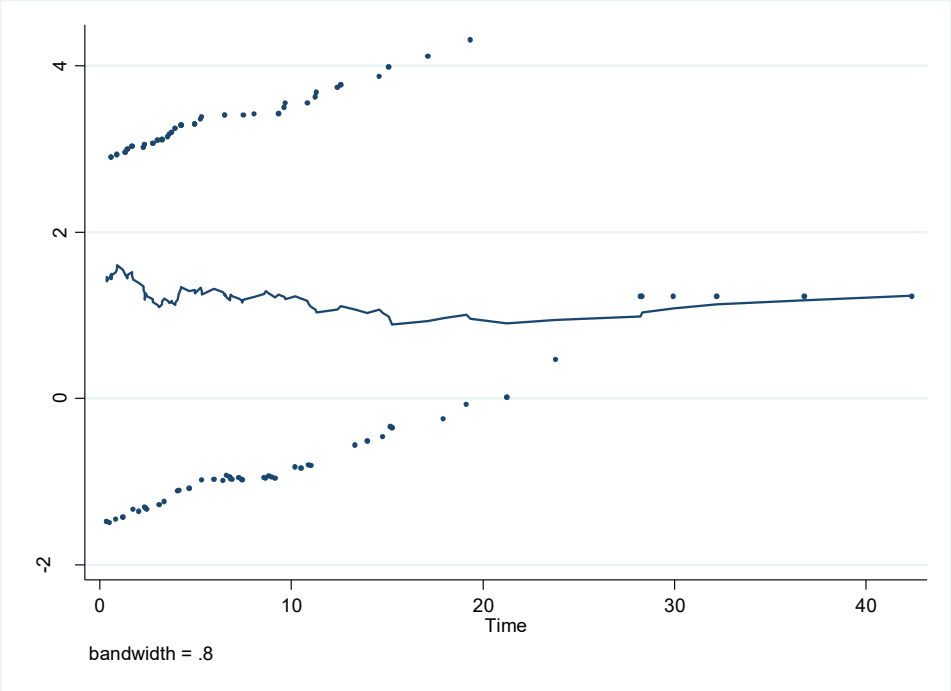
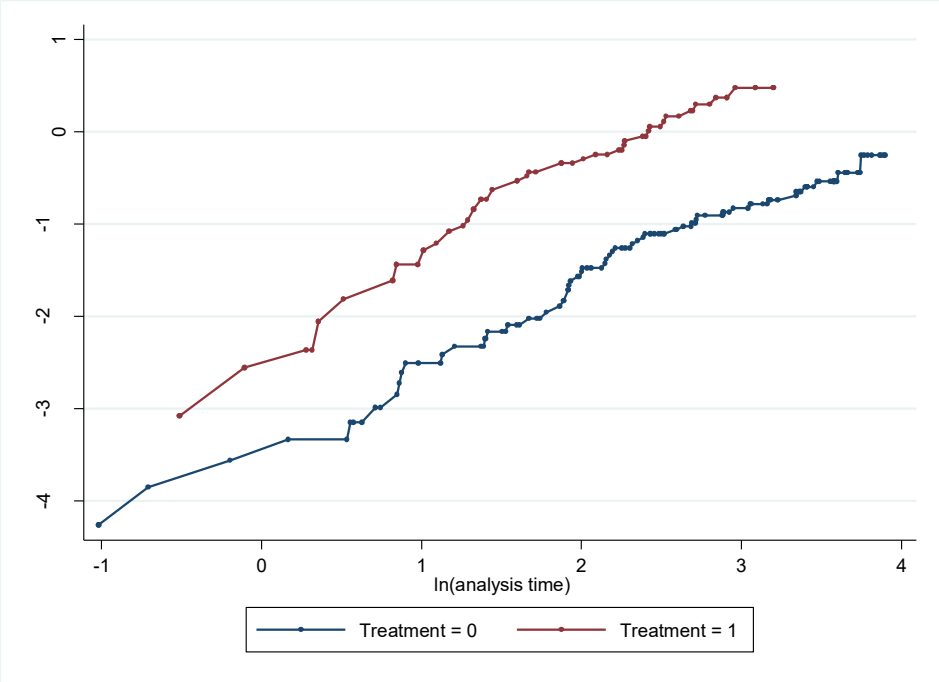


Figure 17 Comparison of overall survival for ELIANA and ENSIGN

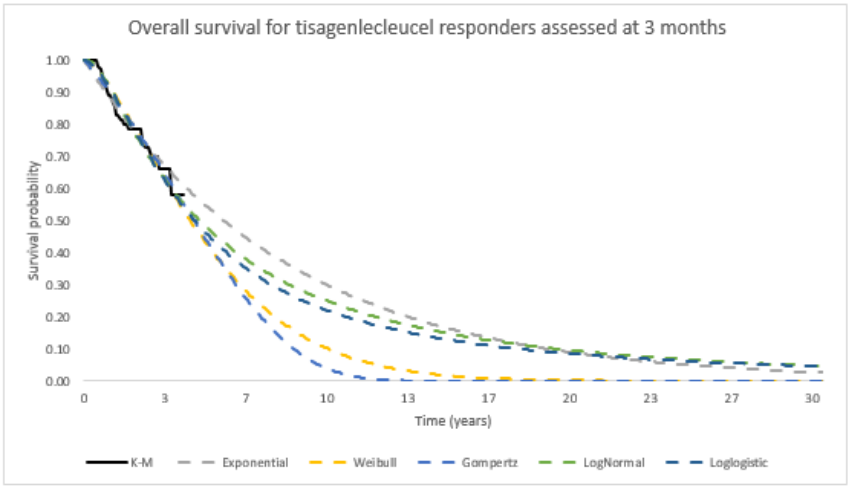


A



B

Figure 18 Scaled Schoenfeld residuals for overall survival by treatment (A) and OS TTNR log(-log(S)) versus log(time) by treatment (tisagenlecleucel and blinatumomab)



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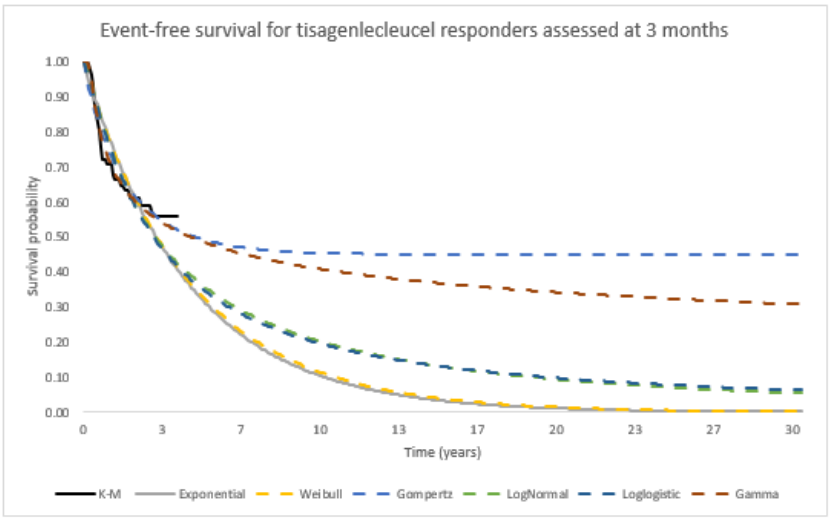

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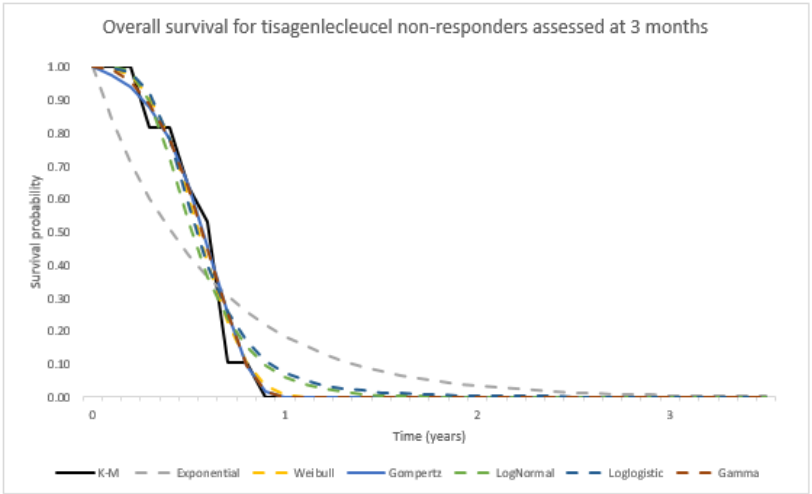


C

Figure 19 Independent parametric models for tisagenlecleucel; overall survival for responders (A), non-responders (B), and event-free survival for responders (C) assessed at 3 months

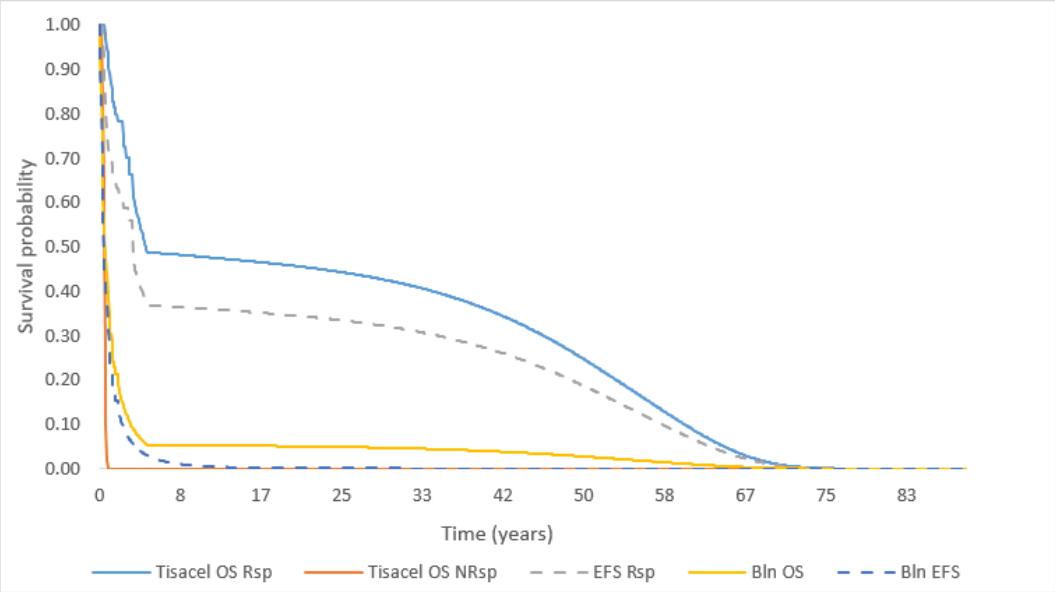


Figure 20 Modelled overall survival and event-free survival for tisagenlecleucel compared with blinatumomab (base case analysis at 3-month response assessment)

Supplementary Tables

Table 13 Patient numbers for each sub-group at each time point compared with the overall cohort

	3 months				12 months			
Study	ELIANA	ENSIGN	Total	Proportion	ELIANA	ENSIGN	Total	Proportion
Enrolled	97	75	172	-	97	75	172	-
Non-infused	18	11	29	0.17	18	11	29	0.17
Infused	79	64	143	0.83	79	64	143	0.83
Responders	64	42	106	0.74	32	24	56	0.39
Non-responders	4	7	11	0.08	1	1	2	0.01
SCT	5	5	10	0.07	16	9	25	0.17
Dead	6	7	13	0.09	16	20	36	0.25
Lost to follow-up	0	3	3	0.02	14	10	24	0.17

SCT denotes stem cell transplant.

Table 14 Disutilities applied in the base case economic model

Event	Utility	Duration (months)	Proportion of patients	Average QALY loss	Source
Tisagenlecleucel					
Grade 3/4 CRS	-0.80	10.3	48.1%	-0.0109	ELIANA[23]; expert opinion
Other serious AEs	-0.10	1.0	89.9%	-0.0075	ELIANA[23]; Sung[144]
Subsequent SCT	-0.57	12.0	5.8%	-0.0331	ELIANA[23]; Casado[143]
Blinatumomab					
Grade 3/4 CRS	-0.80	10.3	5.7%	-0.0013	Von Stackelberg[85]; Assumption
Other serious AEs	-0.10	1.0	87.1%	-0.0073	Von Stackelberg[85]; Sung[144]
Subsequent SCT	-0.57	12.0	34.3%	-0.1955	Von Stackelberg[85]; Casado[143]

AE denotes adverse event; CRS, cytokine release syndrome; SCT, stem cell transplant; QALY, quality adjusted life year.

Table 15 Tisagenlecleucel administration and adverse event management costs

Procedure	% use	Unit cost	No. units	Average	Source
Administration costs					
Leukapheresis	100%	$4,722	1.00	$4,722	AR-DRG R03C, NHCD[195]
Bridging chemotherapy[1]	86.7%	$545	1.00	$632	ELIANA[23]; PBS[147]

Bridging chemotherapy administration	86.7%	$323	5.00	$1,398	Item 1011, NHCD[195]
Lymphodepleting chemotherapy[2]	96.0%	$254	1.00	$254	ELIANA[23]; PBS[147]
LDC inpatient administration	65.3%	$1,426	15.84	$14,756	ELIANA[128]; AR-DRG 60A/B, NHCD[195]
LDC outpatient administration	34.7%	$323	4.00	$447	Item 1011, NHCD[195]
TIS inpatient administration	94.7%	$1,426	30.36	$40,982	ELIANA[128], AR-DRG 60A/B NHCD[195]
TIS outpatient administration	5.3%	$323	1.00	$17	ELIANA[128], Item 1011, NHCD[195]
Adverse event costs					
ICU for CRS	48.1%	$3,793	11.10	$20,250	ELIANA[23], Hicks[196]
Tocilizumab for CRS	39.2%	$378	1.68	$249	ELIANA[23], PBS[147]
IVIg use for B-cell aplasia[3]	88.0%	$968	1.00	$852	ELIANA[23], NBA[197]
IVIg administration[3]	88.0%	$323	1.00	$284	Item 1011, NHCD[195]
Other serious adverse events	89.9%	$947	7.00	$5,953	ELIANA[23]; AR-DRG X62A/B, NHCD[195]

AR-DRG denotes Australian Refined Diagnosis Related Groups; CRS, cytokine release syndrome; ICU, intensive care unit; IVIg, intravenous immunoglobulin; LDC, lymphodepleting chemotherapy; NBA, National Blood Authority; NHCD, National Hospital Cost Data; PBS, Pharmaceutical Benefits Scheme; TIS, tisagenlecleucel.
[1]Cytarabine, vincristine, etoposide, idarubicin, methotrexate
[2]Fludarabine & cyclophosphamide; cytarabine & etoposide
[3]Monthly cost applied for an average treatment duration of 36 months.

Table 16 Blinatumomab drug costs

Cycle	Dose	Cost per cycle	% use	Average cost	Source
Cycle 1	5-15 mg/m² daily for 28 days	$32,756	96%	$49,127	Von Stackelberg[85]; PBS[147]
Cycle 2	15 mg/m² daily for 28 days	$39,291	31%		
Cycle 3	15 mg/m² daily for 28 days	$39,291	10%		
Cycle 4 & 5	15 mg/m² daily for 28 days	$39,291	4%		

Table 17 Blinatumomab administration and adverse event management costs

Procedure	% use	Unit cost	No. units	Average	Source
Administration costs					

Inpatient administration	100%	$1,426	9.26	$13,204	Von Stackelberg[85]; AR-DRG R60A/B, NHCD[195]
Outpatient administration	100%	$323	0.18	$58	Von Stackelberg[85]; Item 1011, NHCD[195]
Adverse event costs					
ICU for CRS	5.7%	$3,793	11.10	$2,400	Von Stackelberg[85], Hicks[196]
Tocilizumab for CRS	5.7%	$378	1.68	$36	Von Stackelberg[85]; PBS[147]
IVIg use for B-cell aplasia[1]	30.0%	$968	1.00	$290	Von Stackelberg[85], NBA[197]
IVIg administration[1]	30.0%	$323	1.00	$97	NHCDC Tier 2 Item 1011
Other serious adverse events	87.1%	$1,530	7.00	$5,772	Von Stackelberg[85]AR-DRG X62A/B, NHCD[195]

AR-DRG denotes Australian Refined Diagnosis Related Groups; CRS, cytokine release syndrome; ICU, intensive care unit; IVIg, intravenous immunoglobulin; LDC, lymphodepleting chemotherapy; NBA, National Blood Authority; NHCD, National Hospital Cost Data; PBS, Pharmaceutical Benefits Scheme

[1]Monthly cost applied for an average treatment duration of 36 months.

Table 18 Health state costs

Health states	Cost	Source
Event-free survival	$847	Muszbek[149]
Progressive disease	$6,334	

Table 19 OBA scenario analyses results (3-month response assessment)

	Incremental costs	Incremental QALYs	ICER	% Change ICER	Financial impact[1]
Base case[2]	$379,595	4.27	$88,979	-	-
0.97 RR	$408,173	5.26	$77,599	-12.8%	$2,857,757
0.65 RR	$351,018	3.27	$107,273	20.6%	-$2,857,757
Split					
0.97 RR	$434,740	5.26	$82,650	-7.1%	$5,514,492
0.65 RR	$324,450	3.27	$99,154	11.4%	-$5,514,492
Responders only					
0.97 RR	$470,423	5.26	$89,434	0.5%	$9,082,757
0.65 RR	$288,768	3.27	$88,249	-0.8%	-$9,082,757

ICER denotes incremental cost-effectiveness ratio; QALY, quality adjusted life year; RR, response rate.

[1]Change from base case assuming a population size of 100 patients over a lifetime

Table 20 Sensitivity analysis results (3-month response assessment)

Sensitivity	Incremental costs	Incremental QALYs	ICER	% Change ICER
Base case	$379,595	4.27	$88,979	
Discount rate				
1.5%	$441,733	7.66	$57,660	-35.2%
3.5%	$398,933	5.31	$75,081	-15.6%
"Cure point"				
2 years	$287,518	4.58	$62,718	-29.5%
10 years	$358,543	3.09	$116,206	30.6%
Parametric equation				
Gompertz	$318,403	4.19	$76,018	-14.6%
Exponential	$435,327	4.63	$94,049	5.7%
Duration IVIg use (years)				
2.42	$376,129	4.27	$88,167	-0.9%
3.58	$382,580	4.27	$89,679	0.8%
80.00	$449,439	4.27	$105,351	18.4%
Proportion SCT[3]				
0	$367,544	4.27	$86,052	-3.3%
0.27	$406,377	4.25	$95,509	7.3%
HR OS: EFS				
0.76	$375,075	4.28	$87,600	-1.5%
0.99	$390,784	4.23	$92,437	3.9%
Long-term SMR				
7.24	$380,813	4.33	$87,848	-1.3%
10.86	$378,496	4.20	$90,031	1.2%
Proportion IVIg use				
0.70	$374,976	4.27	$87,897	-1.2%
1.00	$382,829	4.27	$89,737	0.9%
KM extrapolation point				
TIS[1]	$380,446	4.25	$89,511	0.6%
BLN[2]	$379,559	4.26	$89,008	0.0%
Proportion infused				
1.00	$457,344	5.13	$89,097	0.1%
0.66	$301,847	3.40	$88,862	-0.1%

EFS denotes event-free survival; ICER; incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year; SCT, stem cell transplant; SMR, standardised mortality ratio.
[1]Applied at 20 months to OS and EFS
[2]Applied at 13 months to OS and EFS
[3]As a proportion of responders

Appendix 2

Supplementary Text

Analysis of tisagenlecleucel individual patient data

Time in PFS for responders at 3 months was estimated from the EFS data for patients who achieved a CR or CRi between 2 and 4 months. A 30-day window either side of the 3-month response time point was included to reflect the variability in timing of response assessments in clinical practice. In the studies, clinical assessments were conducted monthly for the first 6 months, consequently at the 3-month time point (61-122-day period) there was potential for duplicate patient entries as patients could have been assessed up to 3 times. To eliminate duplicate patient entries, only the last assessment during the 61 – 122-day period was included.

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 relapsed. OS was measured from the time patients lost response until end of follow. For non-responders, time in PD was estimated from the OS data for non-responders at 3 months. Non-responders were patients not in CR/CRi at the specified timepoint and included patients who had never achieved a CR/CRi or had achieved a CR/CRi prior to the specified timepoint but had subsequently relapsed.

Analyses used data censored for SCT to allow for sensitivity analysis on different rates of subsequent SCT post infusion with tisagenlecleucel. Data for patients who received SCT following infusion with tisagenlecleucel were not analysed separately due to small patient numbers, and SCT censored data were applied to this patient group.

Analysis of the relationship between wait-time and overall survival

To determine whether the clinical trial data demonstrated an impact of wait-time on post-infusion survival, data for wait-time was matched to duration of OS for individual patients from the

ELIANA and ENSIGN trials. Linear regression was applied to wait-time as the independent variable and overall survival as the dependent variable. The results showed no linear relationship between wait-time and duration of OS (adjusted R^2 = -0.007; p-value = 0.793; Figure 22), indicating that there was no association between CAR-T wait-time and OS benefit. Therefore, no adjustment was made to the survival distributions post-infusion to account for impact of wait-time on infused patients (Supplementary Table 23).

Impact of OBAs on cost-effectiveness uncertainty

Two different response-based payment structures were considered: 1) split payment; payment 1 on infusion and payment 2 on response, or a smaller payment where patients could not be assessed for response (lost to follow-up), 2) single payment on response only. The amount per payment was weighted by the proportion of responders and non-responders to equal a weighted price of $375,000 for each scenario. An equal weighted price was maintained across each OBA scenario because the purpose of the analysis was to test the impact of different payment structures, as opposed to the impact of a lower net price. To assess the impact of the OBA scenarios on the ICER, the proportion of patients in response was varied by ± 20% and rates of non-response, dead and lost-to-follow-up were varied proportionally.

Supplementary Tables

Table 21 Utility values for PFS and PD health states derived from EQ-5D data from the ELIANA clinical trial

Health States	N patients[1]	N assessments	Mean	SD
PFS	29	130	0.81	0.18
PD	31	48	0.69	0.25
Relapsed state before treatment	31	31	0.65	0.24
Post-EFS	10	17	0.78	0.26

PD denoted progressive disease; PFS, progression-free survival; SD, standard deviation.
[1] The same patient can have multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state

Table 22 Proportion of patients died, experienced manufacturing failure of an AE at the pre-infusion phase of the model (base-case)

Time (months)	Enter model	Dead	Manufacture fail	Adverse event
0	1.000	0.021	0.079	0.005
1	0.806	0.066	0.079	0.013
2	0.161	0.074	0.079	0.019
3	0.023	0.075	0.079	0.024
4	0.006	0.075	0.079	0.026
5	0.003	0.075	0.079	0.027
6	0.002	0.075	0.079	0.028
7	0.001	0.075	0.079	0.028
8	0.001	0.075	0.079	0.028
9	0.000	0.075	0.079	0.029
10	0.000	0.075	0.079	0.029

Note: The “Enter model” column represents the proportion of patients in the pre-infusion phase of the model. By 2 months most patients have exited the pre-infusion phase because they have either been infused, died, experienced a manufacturing fail or adverse event. The “dead”, “manufacture fail” and “adverse event” columns show the proportion of patients who have experienced each of these events during the pre-infusion phase of the model.

Table 23 Results of the OBAs at different response rates

	Incremental cost				Cost per QALY		
Proportion patients in response	Payment on infusion (base)	Split payment[1]	Responder only[2]	Incremental QALYs	Payment on infusion (base)	Split payment	Responder only
0.65	$411,224	$384,689	$348,596	3.52	$116,957	$109,410	$99,145
0.81	$441,652	$441,209	$440,274	4.60	$96,074	$95,978	$95,774
0.97	$473,798	$501,777	$539,894	5.73	$82,629	$87,508	$94,155

[1] Payment of $206,271 on infusion and a second payment of $206,271 on response or $82,508 on lost to follow-up.
[2] Single payment of $462,963 on response only

Supplementary Figures

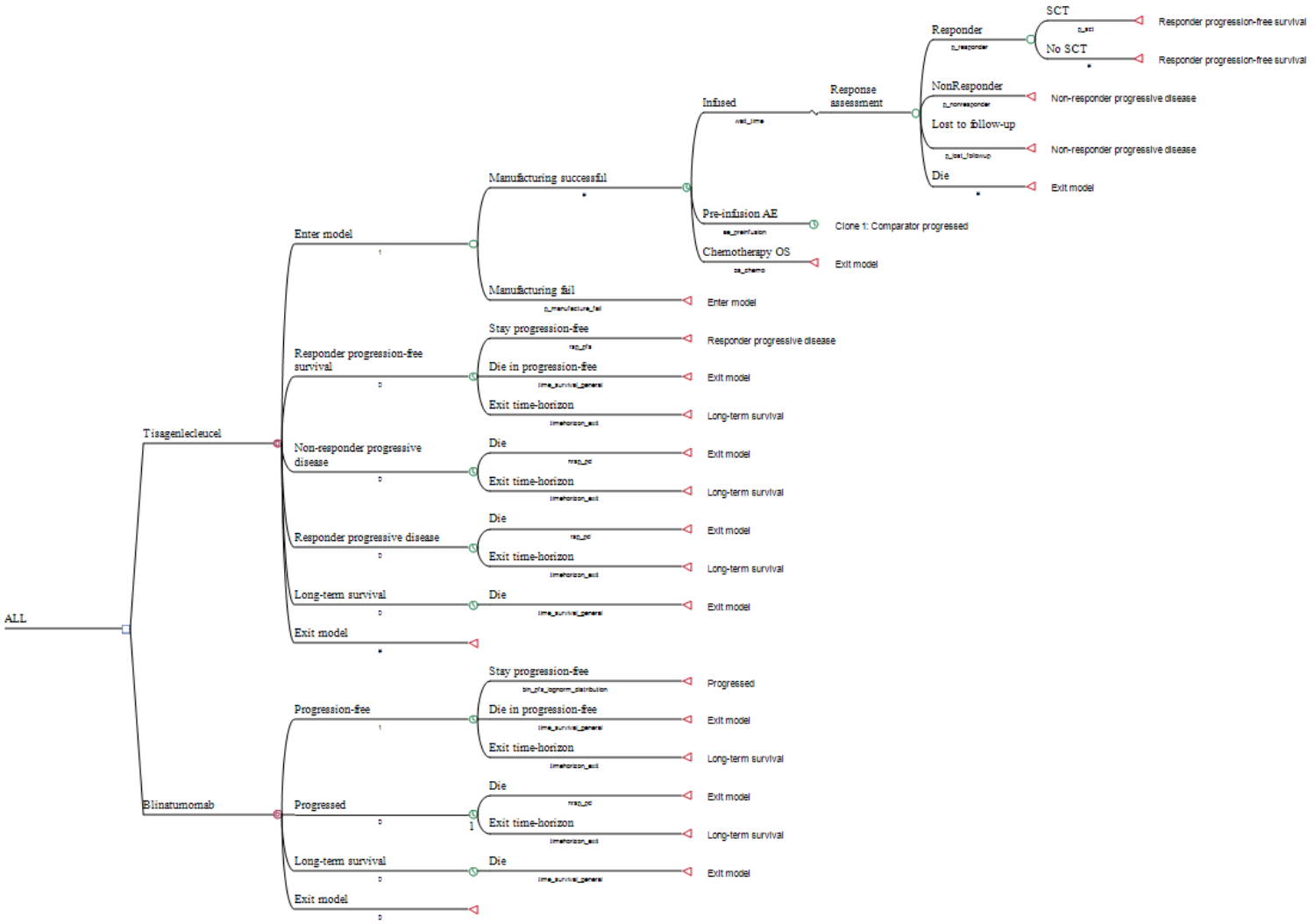


Figure 21 Model structure

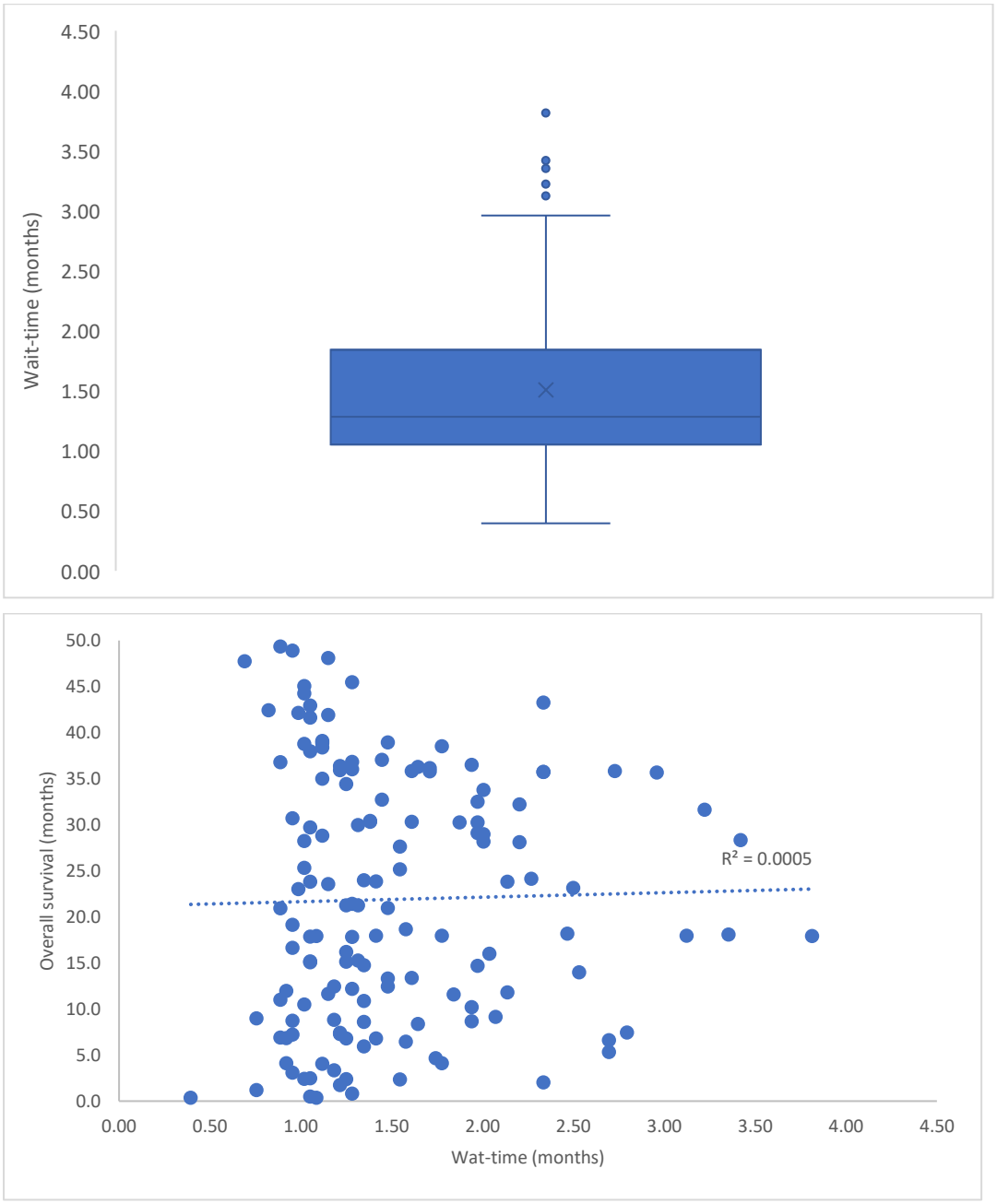


Figure 22 (A) Box plot showing distribution of CAR-T wait-time in ELIANA and ENSIGN trials, highlighting the mean and outliers; (B) Scatter plot and regression line with wait-time as the independent variable and overall survival as the dependent variable for enrolled patients in the ELIANA and ENSIGN trials.

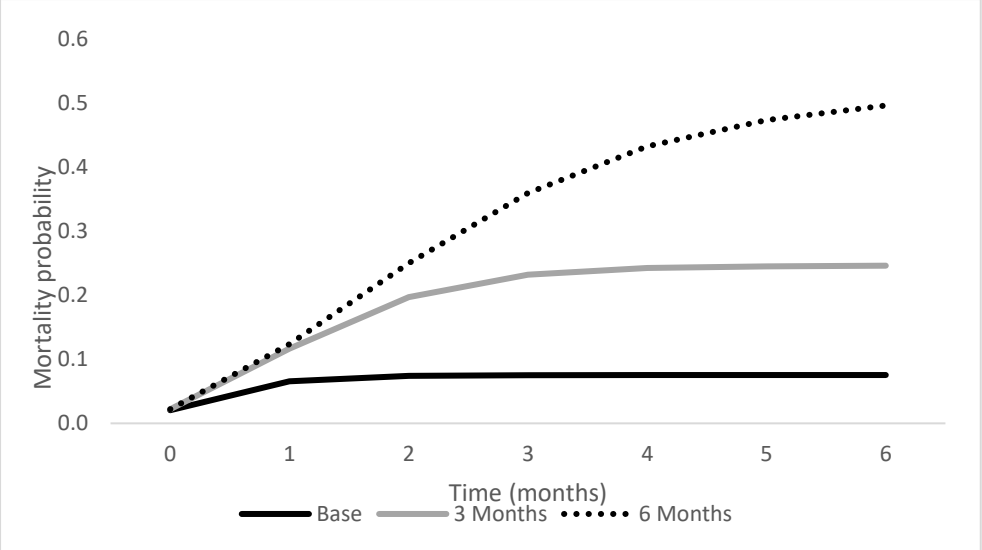


Figure 23 Mortality probability during CAR-T wait-time at base case, 3 months and 6 months average wait-time

Note: Data represent mean mortality at each time point generated from the model using OS data sourced from von Stackelberg et al 2011[170] to estimate mortality risk at 3-month and 6-month wait-time periods. Mortality probability for the base-case was based on the ELIANA trial.

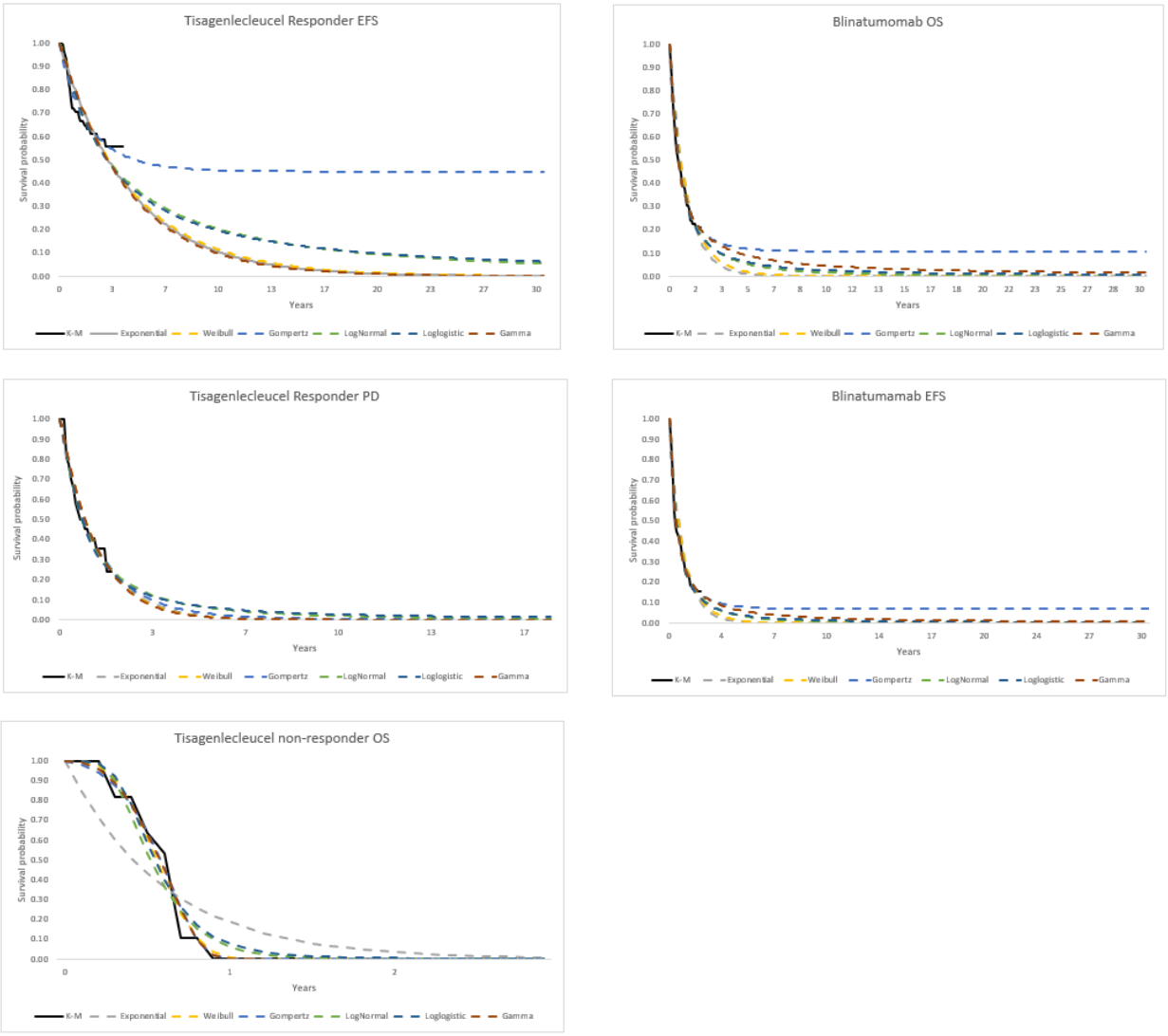
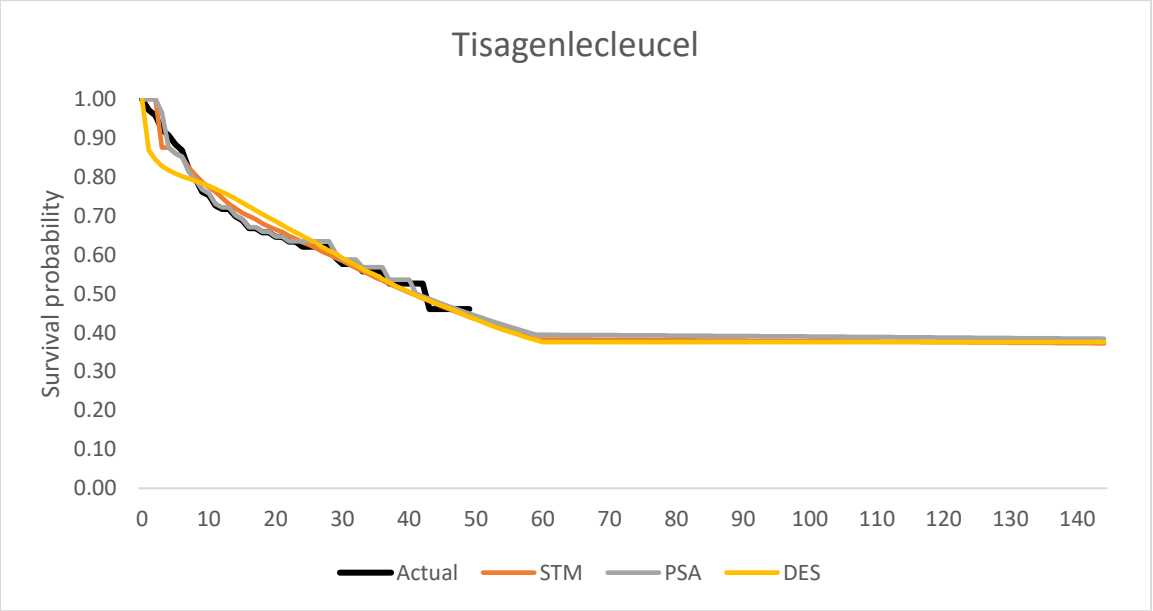


Figure 24 Parametric survival curves for tisagenlecleucel post-infusion and blinatumomab

Appendix 3

Supplementary Figures



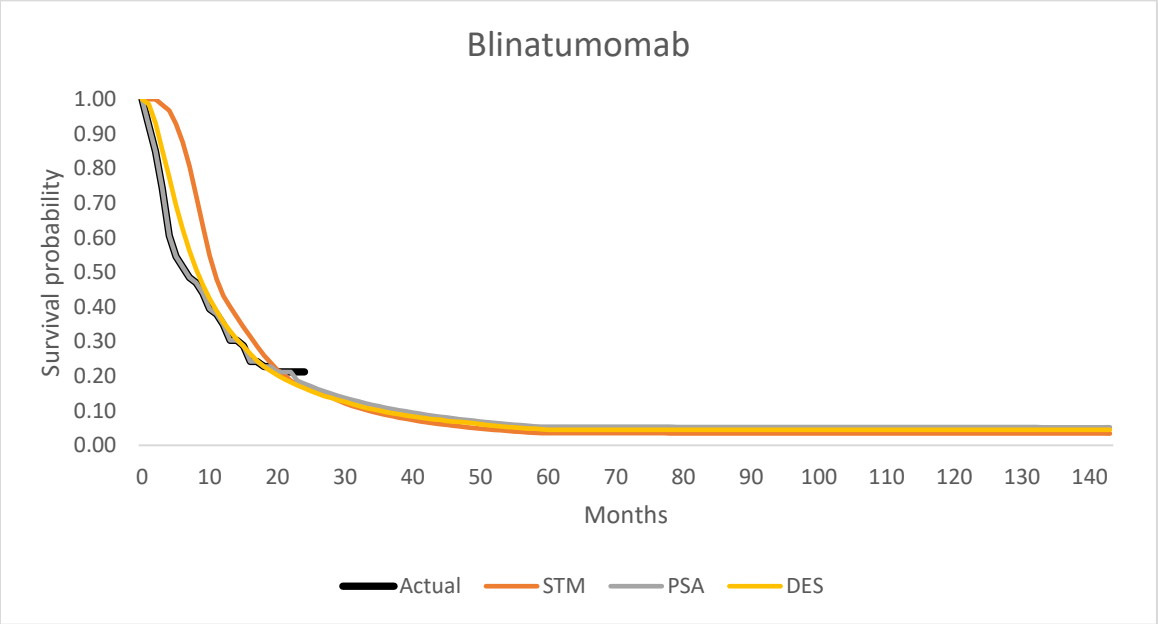


Figure 25 OS curves for tisagenlecleucel and blinatumomab for the observed data versus modelled using STM, PSM and DE

Supplementary Tables

Table 24 Comparison of model methods

		STM	**PSM**	**DES**
Specification	Software program	Microsoft Excel	Microsoft Excel	Treeage
	Cycle length	Monthly time units	Monthly time units	Discrete time units
	Time horizon	Lifetime	Lifetime	Lifetime
	Discount rate	5% costs and benefits	5% costs and benefits	5% costs and benefits
Pre-infusion phase	Infusion wait-time	Not captured	Not captured	Infusion wait-time estimated from IPD data for the period between leukapheresis and enrolment. Incorporated OS data for chemotherapy to estimate risk of mortality during wait-time period.
	Pre-infusion events (death/AEs, manufacturing failure)	Independent of wait-time	Independent of wait-time	Dependent on wait-time. Mortality risk from OS distribution using external data source for chemotherapy. AEs and manufacturing from clinical trials.
	Re-manufacturing	Not captured	Not captured	Patients who did not proceed to infusion due to

				manufacturing failure could re-enter the model
Post-infusion phase	OBA	Incorporated response assessment at 3 months for OBA	Incorporated response assessment at 3 months for OBA	Incorporated response assessment at 3 months for OBA
	Health states	Movement of patients from PFS to PD determined by transition probabilities using post-progression survival data (patients in response at 3 months who subsequently lost response)	Movement of patients from PFS to PD derived by the difference between EFS and OS	Movement of patients from PFS to PD determined by time-to-event probability distribution using post-progression survival data.
	Movement between health states	Proportion of patients in responder PFS derived from EFS for patients in response at 3 months	Proportion of patients in responder PFS derived from EFS for patients in response at 3 months	Proportion of patients in responder PFS derived from EFS for patients in response at 3 months
		Proportion of patients in non-responder PD derived from OS for patients in non-response at 3 months	Proportion of patients in non-responder PD derived from OS for patients in non-response at 3 months	Proportion of patients in non-responder PD derived from OS for patients in non-response at 3 months
		Proportion of patients who move from responder PFS to responder PD derived from post-progression OS (patients	Responder PD derived from the difference between responder EFS and OS	Proportion of patients who move from responder PFS to responder PD derived from post-progression OS (patients

		in response at 3 months who subsequently lost response)		in response at 3 months who subsequently lost response)
		OS informed by the transition of patients from PFS to PD	OS independent of PD	OS informed by the transition of patients from PFS to PD
	Long-term survival	SMR adjusted all-cause mortality applied at 5 years to patients in PFS and PD	SMR adjusted all-cause mortality applied at 5 years to patients in PFS and PD	SMR adjusted all-cause mortality applied at 5 years to patients in PFS and PD in "long-term" health state
		Ability to apply different cure-point assumptions by health state.	Model not conducive to the application of different cure-point assumptions by health state.	Ability to apply different cure-point assumptions by health state.
		Long-term survival linked to average age of the cohort	Long-term survival linked to average age of the cohort	Long-term survival linked to individual age
Costs and benefits	Utilities	No pre-infusion wait-time utility	No pre-infusion wait-time utility	Pre-infusion utility assigned to infusion wait-time period
		PFS and PD health state utilities	PFS and PD health state utilities	PFS and PD health state utilities
	Costs	Assigned an average aggregate cost for tisagenlecleucel	Assigned an average aggregate cost for tisagenlecleucel	Tisagenlecleucel costs disaggregated at the point of leukapheresis, bridging chemotherapy and infusion.

AE indicates adverse event; EFS, event-free survival; IPD, individual patient data; OBA, outcomes-based payment arrangement; OS, overall survival; m, months; PD, progressive disease; PFS, progression-free survival; SMR, standardized mortality ratio.

Table 25 Sensitivity analysis results

	Incremental costs			Incremental QALYs			ICER		
	STM	**PSM**	**DES**	**STM**	**PSM**	**DES**	**STM**	**PSM**	**DES**
Base-case	**$414,726**	**$420,107**	**$441,652**	**4.16**	**4.24**	**4.6**	**$99,625**	**$99,038**	**$96,074**
Discount rate									
1.50%	$498,841	$499,258	$567,605	7.63	7.65	9.5	$65,395	$65,265	$59,748
Cure assumptions									
Cure-point removed	$356,681	$370,343	$378,026	2.22	2.37	2.38	$160,841	$156,104	$158,702
Cure-point PFS only	$369,169	n/a	$384,136	3.81	n/a	3.9	$96,915	n/a	$98,475
Cure-point (2 yrs)	$425,992	$392,669	$494,323	5.14	4.31	6.07	$82,921	$91,053	$81,421
Cure-point (10 yrs)	$363,821	$387,580	$396,778	2.77	3.07	3.25	$131,283	$126,132	$122,057
CAR-T wait-time									
0 months	n/a	n/a	$508,350	n/a	n/a	5.1	n/a	n/a	$99,602
6 months	n/a	n/a	$113,259	n/a	n/a	1.59	n/a	n/a	$71,112
IVIg duration									
None	$391,932	$397,055	$405,236	4.16	4.24	4.6	$94,149	$93,603	$88,153
Lifetime	$494,859	$502,618	$558,428	4.16	4.24	4.6	$118,874	$118,489	$121,477
Payment arrangements									
Single, on successful infusion									
RR 0.65	$378,365	$385,905	$411,224	3.14	3.23	3.52	$120,408	$119,337	$116,957
RR 0.97	$451,087	$454,310	$473,798	5.18	5.25	5.73	$87,025	$86,535	$82,629
Split-payment OBA									
RR 0.65	$350,630	$359,338	$384,689	3.14	3.23	3.52	$111,582	$111,121	$109,410

RR 0.97	$478,822	$480,877	$501,777	5.18	5.25	5.73	$92,376	$91,595	$87,508
Response-only payment OBA									
RR 0.65	$316,115	$323,655	$348,596	3.14	3.23	3.52	$100,598	$100,086	$99,145
RR 0.97	$513,337	$516,560	$539,894	5.18	5.25	5.73	$99,035	$98,392	$94,155

CAR-T indicates chimeric antigen-receptor T-cell therapy; ICER, incremental cost-effectiveness ratio; m, months; PFS, progression-free survival; IVIg, intravenous immunoglobulin; yrs., years.

Appendix 4

Table 26 Published cost-effectiveness analyses of CARTs and incorporation of different payment approaches

Study	Country	Economic model	Payment approaches	Results	Comments
Tisagenlecleucel ALL					
Furzer et al 2020[151]	Canada	Microsimulation	• Payment for those infused and achieving remission within 1 month (base case).	Removal of OBP increased ICER (20% change from baseline)	
Hettle et al 2017[9]	UK	Bridge to transplant	• Lifetime leasing; monthly payments while the patient remains alive • Pay for performance; retrospective payment for patients who achieved remission within 28 days or rebate for patients who do not achieve remission. • Fixed price discount	Base case ICER: £55,090 Lifetime leasing ICER: £54,227 Pay for performance (70% on average) ICER: £36,430 Fixed price discount (10%): £49,857	The panel considered the different pricing schemes had important impacts on the ICER. Leasing approach considered an important option – requires further exploration (logistics, costs, overall feasibility). Innovative financing schemes could be an important consideration in future appraisals.
Hettle et al 2017[9]	UK	Curative intent PSM		Base case ICER: £50,906 Lifetime leasing ICER: £50,618	

				Pay for performance (90% on average) ICER: £45,708 Fixed price discount (10%): £45,131	
Lin et al 2018[61]	US	Markov cohort model	• Payment for those infused and achieving remission within 1 month (base case)	OBA did not materially affect economic value when compared with no OBA (all patients pay) due to high initial remission rates. Varying remission duration threshold - Increasing payment for remission duration to 7 months improved the ICER (within $100,000/QALY threshold US).	Increasing the remission duration threshold resulted in the therapy becoming more economically attractive.
Sarkar et al 2019[150]	US	Microsimulation	• Payment for those infused and achieving remission within 1 month (base case)	When cost of tisagenlecleucel is applied to all patients ICER increased to $75,600 PER QALY (from a base case of $64 400) USD.	Expensive innovative systemic therapies will require equally innovative payment models, such as OBAs, incremental payments over time, indication specific pricing or models that defer part of the payment until the drug is

					confirmed to be efficacious with long-term follow-up.
Whittington et al 2018[132]	US	PSM with preceding decision tree	• Payment only for responders at 1 month (base case).	ICER 46,000 USD per QALY.	Novel payment models consistent with the present evidence may reduce the risk and uncertainty in long-term value and be more closely aligned with ensuring high value care.
Tisagenlecleucel DLBCL					
Lin et al 2019[152]	US	Markov model	• Payment for initial CR • Payment for CR or PR at 3 months	ICER range: 88,300 – 174,000 USD per QALY vs base-case range: 168,000 – 337,000 per QALY. Payment for initial response improved cost-effectiveness.	Payers and sponsors could negotiate innovative reimbursement arrangements to tie payment to outcomes. Price reductions or payment for initial response could improve cost-effectiveness, even with modest long-term outcomes.
Axicabtagene ciloleucel, DLBCL					
Lin et al 2019[152]	US	Markov model	• Payment for initial CR • Payment for CR or PR at 3 months	ICER range: 90,500 – 135,000 USD per QALY vs base-case range: 129,000 – 194,000 per	Payers and sponsors could negotiate innovative reimbursement arrangements

				QALY. Payment for initial response improved cost-effectiveness.	to tie payment to outcomes. Price reductions or payment for initial response could improve cost-effectiveness, even with modest long-term outcomes.

ALL denotes acute lymphoblastic leukaemia; CR, complete remission; PR, partial remission; ICER, incremental cost-effectiveness ratio; OBA, outcomes-based payment arrangement; PSM, partitioned survival model; QALY, quality adjusted life year.

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