**Tisagenlecleucel for the Treatment of Relapsed or Refractory B-cell Acute Lymphoblastic Leukaemia in People Aged up to 25 Years: an Evidence Review Group Perspective of a NICE Single Technology Appraisal**

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**Running heading:**

Tisagenlecleucel for treating r/r B-cell ALL in under-25s: an ERG Perspective

Abstract

As part of the National Institute for Health and Care Excellence’s (NICE) Single Technology Appraisal (STA) process, Novartis submitted evidence on the clinical- and cost-effectiveness of tisagenlecleucel for treating paediatric and young adult patients (under the age of 25 years) with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL). This article presents a summary of the Evidence Review Group’s (ERG) independent review of the evidence submission, the Committee’s deliberations, and the subsequent development of NICE guidance for the use of tisagenlecleucel on the NHS in England. Tisagenlecleucel is a chimeric antigen receptor-modified T-cell (CAR-T) product, the first of this emerging therapeutic class to be considered by NICE in this indication. The company’s evidence submission was based upon three single arm phase II studies: ELIANA, ENSIGN, and B2101J. These trials demonstrated a beneficial effect of tisagenlecleucel, with significant extensions in event-free survival (EFS) and overall survival (OS) compared to historical control datasets on blinatumomab and salvage chemotherapy. Adverse events were common; 77% of patients suffered from cytokine release syndrome, 56% of whom required ICU-level care. The ERG did not consider clofarabine monotherapy an appropriate proxy for salvage chemotherapy. The company presented a hybrid cost-effectiveness model, combining a decision tree and three state partitioned survival model structure. The majority of quality-adjusted life-years (QALYs) gained were generated through additional life years in the extrapolated ‘long-term survival’ phase of the model, where patients were assumed to be ‘cured’. The ERG considered the results to be subject to substantial uncertainty, due in part to immature trial data, unresolved long-term treatment effects, and a lack of appropriate comparator data. The ERG implemented a number of changes to the company’s model in an alternative base-case, producing deterministic incremental cost-effectiveness ratios (ICERs) of £45,397 per QALY gained versus salvage chemotherapy, and £27,732 versus blinatumomab. The probabilistic model produced ICERs of £48,265 per QALY gained versus salvage chemotherapy, and £29,501 versus blinatumomab. The committee considered the ERG’s analysis to be most closely aligned with their preferred assumptions, and did not consider tisagenlecleucel to meet both of the end-of-life (EoL) criteria. In recognition of the innovative nature of tisagenlecleucel, and the present immaturity of ongoing clinical trials, the committee considered further data collection would be valuable in resolving uncertainties around OS, the technology’s novel mechanism of action, and the management of cytokine release syndrome (CRS) and B-cell aplasia. The Committee therefore recommended tisagenlecleucel for use in the CDF until the conclusion of the ELIANA study (June 2023).This appraisal highlighted the difficulty of interpreting EoL criteria in the context of curative therapies and the valuation of cure versus extension of life. Further clarification of NICE’s position in these situations may be necessary to ensure consistency and equity in their decision-making.

Key points for decision makers

Tisagenlecleucel appears to be significantly more effective than the current standard of care for the treatment of relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia patients under the age of 25 years, but the technology’s novel mechanism of action and immature overall survival (OS) data mean uncertainties remain around the curative potential of the technology.

The Committee considered the most plausible incremental cost-effectiveness ratios (ICER) for tisagenlecleucel to be over £30,000 but less than £50,000 per quality-adjusted life-year (QALY) gained, but did not consider it to meet both end-of-life criteria, therefore it was not recommended for routine commissioning on the NHS.

The Committee recommended tisagenlecleucel as an option for r/r B-cell acute lymphoblastic leukaemia patients under the age of 25 years for use in the Cancer Drugs Fund, as data collection is likely to resolve uncertainties around long-term efficacy and adverse event management.

NICE’s position on end-of-life may require further clarification in potentially curative therapies to ensure consistency and equity in their decision-making.

# Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing evidence-based guidance to the National Health Service (NHS) in England for a range of health and social care issues. Single Technology Appraisals (STAs) evaluate a single technology with respect to a single indication, and provide recommendations in the form of NICE guidance on the use of technologies in the NHS 1. The company or sponsor of the technology submits the principal evidence supporting the clinical and cost-effectiveness of the product, and an external independent academic organisation, in this case the CRD/CHE Technology Assessment Group, hereafter referred to as the Evidence Review Group (ERG), is commissioned to produce a review and critique of the evidence submitted 2. Consultees, clinical specialists, NHS commissioning experts and patient representatives provide additional information for consideration by the NICE Appraisal Committee when formulating their guidance 1. Once published, NICE technology guidance constitutes a legal obligation for NHS providers to reimburse a technology within its licensed indication.(2, 3)

NICE invited Novartis, the manufacturer of tisagenlecleucel, to submit evidence on the clinical- and cost-effectiveness evidence of tisagenlecleucel for the treatment of paediatric and young adult patients (under the age of 25 years) with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL), as a part of the STA process. This article presents a summary of the ERG’s independent review of the company’s submissions to NICE, the Committee’s deliberations, and the subsequent development of NICE guidance for the use of tisagenlecleucel on the NHS in England. Full details of the relevant appraisal documents, including the appraisal scope, company and consultee submissions, ERG report, and Final Appraisal Determination can be found on the NICE website3.

# Decision Problem

B-cell Acute lymphoblastic leukaemia (ALL) is a common form of paediatric leukaemia, and comprises around 25% of all cancers diagnosed before the age of 15 4. The disease is characterised by an overproduction of immature white blood cells called lymphoblasts 5, as these accumulate and begin to outnumber healthy blood cells they disrupt normal blood and organ function. As an acute cancer, ALL progresses rapidly and if left untreated will result in death. There are around 810 new cases of ALL diagnosed each year in the UK 6, but those who have relapsed 2 or more times, or are refractory to treatment, only comprise around 20-30 new patients per year 7.

There are no published guidelines for the treatment of ALL in the UK in paediatric patients. A number of factors determine therapeutic approach, including age, severity, and previous treatments used 8. First- and second-line treatment for patients historically consisted of multi-drug chemotherapy, with patients experiencing a second relapse after maintenance therapy treated with either salvage chemotherapy (generally FLA-IDA, comprising fludarabine, cytarabine, and idarubicin) or blinatumomab depending on the first-line salvage therapy used 9, 10. The main aim for B-cell ALL patients with two or more relapses is to induce remission, which is consolidated with an allogenic stem cell transplant (allo-SCT). If a patient has recently received an allo-SCT and relapsed, treatment options are limited; palliative care and enrolment in clinical trials are often the only remaining choices 11.

Tisagenlecleucel is a chimeric antigen receptor-modified T-cell (CAR-T) product, the first of this emerging therapeutic class to be considered by NICE in this indication. The manufacturing process involves the collection of effector T-cells from the patient’s blood through leukapheresis, which are then shipped to a manufacturing facility and modified to target the CD-19 antigen found on leukaemic cells. This process generally takes 3-4 weeks, thus most patients will require bridging chemotherapy to stabilise disease progression until the product is prepared. The modified and cultured cells are then infused into the patient in a single session, and can continue to circulate for up to 780 days 12.

Tisagenlecleucel was granted EMA marketing authorisation in June 2018. It is licensed for use in paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse 13. This is the population considered in the company submission (CS), which indicates that tisagenlecleucel should be used in the later stages of the treatment pathway, or in refractory disease.

At the time of the appraisal there were two options recommended by NICE for the treatment of r/r B-cell ALL: salvage chemotherapy, specifically FLA-IDA for paediatric patients and FLAG-IDA (i.e. FLA-IDA plus granulocyte-colony stimulating factor) for patients over 18 years old, or blinatumomab. Inotuzumab ozogamicin has since received a positive recommendation in this population.

# The Independent Evidence Review Group (ERG) Review

The company submitted evidence to NICE on the use of tisagenlecleucel in r/r B-cell ALL in patients aged up to 25 years, the ERG then performed a review of the clinical and cost effectiveness of tisagenlecleucel, based on the evidence provided in the company’s submission. The ERG has three primary roles in their critical review: to assess whether the company’s submission conformed to the methodological guidelines issued by NICE; to assess whether the company’s interpretation and analysis of the evidence were appropriate; to indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform NICE guidance.

## Clinical Evidence

### Summary of Submitted Clinical Effectiveness Evidence

The company conducted a systematic review of studies evaluating the efficacy and safety of tisagenlecleucel for the treatment of r/r B-cell ALL in paediatric and young adult patients. Three ongoing, single-arm, phase II, open-label studies: ELIANA, ENSIGN and B2101J were identified in the review and included in the company submission. All three trials evaluated tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL 14-16, with a median follow-up of between 13.1 months and <3 years. The trials demonstrated a beneficial effect of tisagenlecleucel with significant extensions in event-free survival (EFS) and overall survival (OS) over the usual life expectancy, with a median OS of 37.9 months observed in the B2101J trial. Patients who were enrolled in the trials but were not infused due to manufacture failure or adverse events (AEs) had a very poor prognosis. The exact figures for the ENSIGN and ELIANA trials are currently unpublished and as such cannot be reproduced here.

All relevant trials of tisagenlecleucel were single arm studies with no comparator; the company therefore identified evidence for comparator treatments from published studies. The company used studies by von Stackelberg *et al*. 17 and Jeha *et al*. 18 as evidence on blinatumomab and salvage chemotherapy, respectively. Both studies were phase I/II single-arm, multi-centre, open-label trials, conducted in paediatric r/r B-ALL patients. The von Stackelberg study population comprised patients who are primary refractory, in first relapse after full salvage induction regimen, in second or later relapse, or in any relapse after allo-SCT. In Jeha *et al*. patients were treated with clofarabine therapy, which the company considered an appropriate proxy for salvage chemotherapy, as the CS did not identify any studies evaluating FLA-IDA. The study consisted of 61 patients who received clofarabine intravenously over two hours daily for five days. Comparisons with trials of blinatumomab and clofarabine suggested a strong benefit in terms of both EFS and OS of tisagenlecleucel compared with both blinatumomab and clofarabine.

The company presented a matched-adjusted indirect treatment comparison (MAIC) with data from the pooled tisagenlecleucel population and from the von Stackelberg *et al*. and Jeha *et al*. populations, but these results were not used in the economic model. The hazard ratios show a positive effect of tisagenlecleucel compared to both blinatumomab and salvage chemotherapy.

The safety and tolerability of tisagenlecleucel was evaluated in all three trials, with all patients who received at least one infusion included in the safety population. All patients had at least one AE, and almost all patients had an AE that was suspected to be related to the study-drug. Grade 3 and 4 AEs were reported in 88% of patients. The most common non-haematological adverse reactions of any grades were cytokine release syndrome (CRS) (77%), infections (65%), hypogammaglobulinaemia (47%), and pyrexia (40%).

Cytokine release syndrome can present at any AE grade, ranging from flu-like symptoms to high fever and hypotension, and can lead to circulatory shock, intravascular coagulation, multi-organ system failure, and death if not adequately treated. Treatment with tocilizumab was required in 41.7% of patients, and 56% of patients with CRS required intensive care unit (ICU)-level care; note however that there were no deaths due to CRS recorded in these trials.

The ERG also noted that median time to B-cell recovery had not been reached in any of the trials, suggesting some patients may require long-term treatment with intravenous immunoglobulin (IVIG). In the ELIANA trial, 94.7% of patients had at least one hospitalisation, with many requiring two. Among those patients admitted to hospital, the mean duration of hospitalisation was 29.0 days (range 5 to 214 days). Fifty-three percent of patients were admitted to intensive care, with a median duration of stay of 7 days.

### Critique of Clinical Effectiveness Evidence and interpretation

The systematic review presented in the CS used adequate methods to identify the relevant studies, with no relevant trials likely to have been missed. The three included studies of tisagenlecleucel were of good quality. However, the ERG highlighted some limitations around the representativeness of the patients recruited to the trials. All three trials restricted eligibility to patients with a life expectancy of 12 weeks or more, thus these patients may have been healthier and fitter than the general population of patients at this stage of the treatment pathway. In addition, patients in the B2101J trial were allowed multiple infusions of tisagenlecleucel over several months, a strategy which is not licensed in the UK. This may affect the generalisability of this trial, and as it had the longest follow-up, this may have inflated apparent long-term OS in pooled analysis.

The ERG had several concerns with the analyses presented by the company. The median time between enrolment and infusion of tisagenlecleucel in all three trials was substantially longer than the 3 to 4 weeks estimated in the CS. This may pose a difficult decision for eligible patients due to the speed of disease progression and their short estimated life expectancy, as other treatment opportunities are foregone during this period. In addition, the proportion of patients who received an allo-SCT after infusion in all three trials is concerning considering the curative intent of tisagenlecleucel.

The long-term benefits of tisagenlecleucel were more uncertain than implied by the presented Kaplan-Meier (KM) curves. For those patients successfully infused with tisagenlecleucel, the apparent proportion of patients alive at the most recent follow-up in ELIANA was heavily influenced by censoring of data, and in both ENSIGN and B2101J there are very small numbers of patients at risk beyond 18 and 36 months respectively. Moreover, each trial had notably different proportions of patients alive in the ongoing OS plateaus. Thus, the ERG considered that conclusions about long-term survival and cure should be withheld until more mature data is produced.

The ERG also had concerns regarding the comparability of von Stackelberg *et al*. and Jeha *et al*. trials with the tisagenlecleucel trials, identifying numerous differences in study design and baseline characteristics, and questioning the validity of comparison between what appear to be fundamentally different populations. There was insufficient evidence presented to justify using clofarabine as a proxy for FLA-IDA. The ERG did not consider von Stackelberg *et al*. or Jeha *et al*. as suitable evidence for the comparators.

All comparisons were based on adjusted or unadjusted indirect comparisons, which are prone to bias if adjustment is not perfect and therefore the ERG considered the results of the comparative MAIC analysis to be unreliable.

## Cost-effectiveness Evidence

### Summary of the Cost-effectiveness Evidence

The company’s submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life (HRQoL), and resource use and costs associated with tisagenlecleucel for the treatment of r/r B-cell ALL. This review identified four economic evaluations of tisagenlecleucel, including two models which took a UK perspective 19, 20. These models were based primarily on hypothetical data, and such were not appropriate for estimating the cost-effectiveness of tisagenlecleucel.

The company presented a *de novo* cohort cost-effectiveness model which compared tisagenlecleucel with salvage chemotherapy and blinatumomab in a population of young people with r/r B-cell ALL. Cost-effectiveness was calculated over a lifetime time horizon of 88 years with a 3.5% discount rate applied to both costs and QALYs. A hybrid modelling approach was taken, combining a decision tree and partitioned survival model structure. The decision tree was used to capture the costs and events prior to the point of tisagenlecleucel infusion, after which survival outcomes were determined using the partitioned survival model. This took the same form for all three treatment options, and was based on three health states: event free survival (EFS), progressed disease (PD), and death. Patients receiving either of the comparator therapies spent the duration of the model in the partitioned survival structure.

A central feature of the company’s model was the concept of cure, and the assumption that a proportion of patients treated with tisagenlecleucel proceed to achieve long-term remission and survival. The company modelled this assumption using a fourth health state: long-term survival (LTS). All patients who were alive in either the EFS or PD state at 5 years moved into this health state, in which patients’ quality of life was similar to that of the general population, and individuals incur only nominal costs related to their previous condition. Age-related decline in HRQoL was reflected by applying age-adjusted decrements to the LTS utility value over the modelled time horizon.

The health state utilities selected by the company were 0.91 for those in EFS and LTS, and 0.75 for those in the PD health state. These estimates were derived from a systematic review of utility studies by Kelly *et al.* which converted disease-specific QoL scores to EQ-5D and HUI2. The utility values for event-free survival and long-term survival were derived from a Swiss study26 which generated SF-36 scores for patients diagnosed with ALL between 1976 and 2003, who had been cured following relapse and had survived for at least 5 years. These utility values are based on HUI2, rather than EQ-5D. These estimates were considerably higher than those recorded in the ELIANA trial, which are confidential.

The OS and EFS data for tisagenlecleucel were based on a pooled analysis of the latest available data cuts of three single-arm studies: ELIANA (31st December 2017), ENSIGN (6th October 2017), and B2101J (30th January 2017). This dataset excluded those patients who were enrolled into the trials but did not receive infusion with tisagenlecleucel due to death, adverse events, or manufacturing failure.

Historical control datasets were identified through a systematic review to establish relative effectiveness of tisagenlecleucel compared to blinatumomab and salvage chemotherapy. OS data for blinatumomab were derived from von Stackelberg *et al.* (2016)17, a Phase 1/2 trial which evaluated blinatumomab in a paediatric population with relapsed B-cell ALL. The company did not identify any trials of FLA-IDA in a relevant population, thus the Jeha *et al.* (2006) 18 trial was used to estimate OS, which evaluated clofarabine monotherapy in a primarily paediatric population with r/r B-cell ALL.

To extrapolate the observed OS and EFS data, the company fitted a range of standard parametric models, spline models, and mixture-cure models. The extrapolation selected for tisagenlecleucel in the company’s base-case analysis was a mixture-cure model, wherein mortality rate for the ‘cured’ proportion (fraction) of patients is equal to the age and gender-matched general population mortality rate, while the survival of remaining patients is modelled using a single parametric exponential curve estimated from the trial data. A log-normal function was used as the basis of the mixture-cure model applied to blinatumomab, and a standard (i.e. non-cure) generalised gamma function was used for FLA-IDA. These curves predicted survival rates for five years, after which patients faced an age- and gender-matched general population mortality rate, adjusted using a standardised mortality ratio.

Modelled resource use and costs included: drug acquisition and administration costs, monitoring costs, costs related to health states and adverse events, training costs, and the cost of subsequent treatments (e.g. HSCT). Pre- and post-progression health state costs were estimated using trial data and 2016-17 NHS reference costs 21. While patient access scheme (PAS) discounts are available for tisagenlecleucel, blinatumomab, and the anti-cytokine therapy tocilizumab used to treat CRS, the results reported here include only the PAS for tisagenlecleucel. The Committee’s decision was based upon ICERs which included all relevant confidential PAS discounts.

The company’s analysis found tisagenlecleucel to be more costly and more effective than blinatumomab. The deterministic base-case ICER was £18,392 per QALY gained, while the mean probabilistic ICER was £20,046 per QALY gained. Tisagenlecleucel was found to be more costly and more effective than FLA-IDA, with a deterministic base-case ICER of £25,404 per QALY gained, and mean probabilistic ICER of £27,066 per QALY. The majority of the QALYs gained were generated through additional life years in the LTS phase of the model, where patients were assumed to be ‘cured’. The most influential parameters in the one-way sensitivity analysis was the rate of SCT, and the utilities applied in the EFS health state.

### Critique of the Cost-effectiveness Evidence and Interpretation

The ERG identified a number of key issues regarding the assumptions and data sources adopted by the company in their economic model, which may have affected the estimated cost-effectiveness of tisagenlecleucel. As in many oncology models, the majority of QALYs gained on treatment were accrued over an extended period of extrapolation. The immaturity of follow-up survival data, and the very small numbers of patients at risk in the tail of the KM curves meant that small changes in predicted OS had a significant impact upon the projected long-term benefits, resulting in particular instability in the ICERs produced by this model.

The ERG considered the technology’s novel mechanism of action to present a further layer of uncertainty. Current evidence cannot yet support the extrapolation of survival data based on experience with stem cell transplant, as the persistence of a long-term CAR-T treatment effect is not well characterised. The pivotal trials did not appear to demonstrate healthy B-cell recovery in many (if any) trial patients, thus it is currently unclear how survival curves will develop over longer periods of time.

The ERG considered the extrapolation of survival data based on experience with stem cell transplant subject to substantial uncertainty. The implications of an ~18 month OS plateau in small numbers of patients who may be continuing to benefit from active CAR-T cells (particularly those who received multiple infusions) cannot be considered analogous to a survival plateau seen following a one-off stem-cell transplant, which decades of research have proven to offer a long-term cure. This uncertainty is illustrated by the wide-ranging cure fraction estimates predicted by the alternative mixture cure models, with 35% separating the least and most optimistic predictions of the size of the ‘cured’ population. The company’s base-case analysis used the second most optimistic cure fraction of 44.7%, which the ERG considered clinically unrealistic, given that 40.57% of trial patients achieved long-term event-free survival.

The ERG also noted inconsistencies in the extrapolation of comparator OS data. The application of a cure model to blinatumomab was questionable given the uncertainty in cure fraction estimates (3.9 – 21.7%). The model selected by the company for this comparator was predicted a significantly lower cure fraction (11.4%) than that used in the recent NICE appraisal of blinatumomab in adults (21%); implying a significantly better prognosis in adult patients than in paediatric patients, despite a near identical Kaplan-Meier curve for OS. The ERG considered the fitting of a simple parametric curve to clofarabine monotherapy (salvage chemotherapy) OS data inappropriate, given the use of mixture cure models for the other populations. Cure fractions of 7.2 – 9.4% generated by models for salvage chemotherapy were dismissed by the company as clinically implausible, instead opting for an arbitrary 3% cure rate. The ERG highlighted that the estimated cure fractions of 7.2 – 9.4% were consistent with published literature sources and expert advice, which suggested a 10% cure fraction was reasonable 22, 23.

The ERG did not consider the Jeha *et al*. (2006) trial to be an appropriate basis for informing efficacy estimates for current salvage chemotherapy strategies, due to both the age of the trial and the use of clofarabine, which is not used in UK practice due to its poor clinical outcomes and adverse event profile. Furthermore, other evidence suggests that the long-term survival benefits of blinatumomab relative to salvage chemotherapy are relatively small 24. The substantial differences in short-term OS also led the ERG to suspect there may be important prognostic differences between patients recruited to the tisagenlecleucel trials and those in studies of clofarabine-based regimens considered by the company. The ERG identified two recently published studies on patients with r/r ALL: Sun *et al.*23 (2018) and Kuhlen *et al*.22 (2017), which comprised a substantially larger sample of patients with more mature survival data. These studies corroborated the figure of 10 - 12% long-term survival on salvage chemotherapy, however, the ERG noted that cure fractions across most studies was a relatively constant (~60%) proportion of those who went on to receive a stem-cell transplant. Thus, a more appropriate OS curve may be one adjusted for NHS figures on SCT use in patients on salvage chemotherapy or other systemic agents.

The ERG also highlighted the difficulty in defining current practice in treating ALL patients with 2+ relapses on the NHS, a population perhaps comprising only 20-30 patients per year 7. NICE guidance is already in place for the ~8.3% of patients aged >18 years, who would typically receive blinatumomab as a first-line salvage therapy. This population would not be eligible for blinatumomab again after a second relapse, and therefore its relevance as a direct comparator in this appraisal is unclear. Clinical advice to the ERG and company suggested increasing use of blinatumomab earlier in the treatment pathway in paediatric patients, which may raise the issue of eligibility for tisagenlecleucel after further relapse. Patients who had previously used an anti-CD19 therapy such as blinatumomab were excluded from all three tisagenlecleucel trials, due to the hypothetical impact upon treatment efficacy and the chance of CD19-negative relapse, which was observed in 22% of tested relapses in the paediatric blinatumomab trial 17. This casts some uncertainty upon the relevance of the clinical trial data, as the efficacy of tisagenlecleucel has not been demonstrated in patients previously treated with an anti-CD19 therapy. The Committee also considered the now-approved inotuzumab ozogamicin to further change standard practice at this stage in the treatment pathway.

The ERG also considered the health state utility values included in the company’s base-case to be a potential source of uncertainty. While the company explained that the utility value applied for LTS from Kelly *et al.* is based on patients in EFS, these values were in fact derived from long-term (≥5 years) survivors. It is uncertain whether the utility of cured patients is equivalent to those in short-term EFS; as the 0.91 value was conditional on >5 years of survival this study is likely to have excluded the majority of those patients who initially achieved remission but later relapsed.

Given the complexity of the intervention and patient care needs, the lack of a clear service specification for the production, provision, and administration of tisagenlecleucel on the NHS, there were clear remaining uncertainties regarding the quantification of additional required resource and investment for implementing this intervention on the NHS. The ERG highlighted uncertainty surrounding additional paediatric ICU capacity, which may need to be made available to ensure that patients receiving tisagenlecleucel can be guaranteed access to appropriate services if and when required, without adversely affecting the provision of care to other patients. Uncertainty around the duration of B-cell aplasia, which may require ongoing treatment with expensive intravenous immunoglobulin (IVIG), was also an area of concern.

## Additional work undertaken by the ERG

The ERG undertook a number of exploratory analyses and corrected the application of mortality rates in the model. These analyses related to the key uncertainties previously outlined, and were concerned with the use of alternative OS extrapolations and data sources. The ERG also explored the impact of different levels of prevalence and duration of IVIG use due to ongoing B-cell aplasia and hypo/agammaglobulinaemia. Costs/QALYs for patients who were not successfully infused with tisagenlecleucel were modelled using trial-derived OS data for this group. Further scenarios demonstrated the impact of stem-cell prevalence and disutilities on cost-effectiveness, blinatumomab treatment duration, and usage of ICU beds for patients with cytokine release syndrome.

Following the ERG’s correction to mortality rate calculations, the ICER for tisagenlecleucel increased to £28,806 per QALY gained versus salvage chemotherapy, and £20,864 versus blinatumomab. The exploratory analyses described above produced deterministic ICERs ranging between £26,429 and £41,479 per QALY gained versus salvage chemotherapy, and £17,725 and £29,517 per QALY gained versus blinatumomab. Most scenario analyses resulted in a reduction in the ICER for tisagenlecleucel versus blinatumomab, and substantial increases versus salvage chemotherapy.

The ERG’s alternative base-case analysis incorporated several changes to the company’s model, including the aforementioned mortality calculation correction: the use of Kuhlen *et al.22* (adjusted) as the data source for salvage chemotherapy OS and EFS, the ERG’s preferred OS extrapolations for tisagenlecleucel and blinatumomab; application of ELIANA utility values for tisagenlecleucel patients in EFS and PD for up to two years and Kelly *et al*.25 values for LTS; application of a smaller disutility for patients following SCT; separate modelling of costs and QALYs for patients who did not go on to receive infusion with tisagenlecleucel using ELIANA and ENSIGN OS data; IVIG only used in those patients with hypo/agammaglobulinaemia, patients only receive two cycles of blinatumomab, and incorporates the cost of holding ICU beds during CRS risk period.

The ERG considered this analysis to represent a more plausible estimate of the cost-effectiveness of tisagenlecleucel, and to better reflect the uncertainties around the data and assumptions in the company’s base-case. Based on the tisagenlecleucel PAS price, the deterministic ICERs for the ERG’s alternative base-case analysis were £45,397 per QALY gained versus salvage chemotherapy, and £27,732 versus blinatumomab. The probabilistic model produced ICERs of £48,265 per QALY gained versus salvage chemotherapy, and £29,501 versus blinatumomab.

 The ERG also explored scenarios on the alternative base-case, which assessed the impact of differential rates of SCT and B-cell aplasia duration, these ICERs ranged between £41,274 and £74,322 per QALY gained versus salvage chemotherapy, and £23,900 and £46,133 versus blinatumomab.

# NICE Appraisal Committee

The NICE Appraisal Committee’s initial decision was that tisagenlecleucel should not be recommended for routine on the NHS for treating relapsed/refractory B-cell ALL in people aged up to 25 years. The Committee’s discussion focused on a number of key areas which led them to this first conclusion. Firstly, the Committee were concerned about the lack of clinical evidence on the efficacy of tisagenlecleucel following treatment with blinatumomab, as patients with experience of anti-CD19 therapies were excluded from the pivotal trials due to the possibility of CD19 negative relapse. The committee also did not consider the evidence to sufficiently support the curative nature of tisagenlecleucel, as there is little trial evidence beyond 30 months of follow-up.

The high rates of CRS and the additional requirements for management were also highlighted as an area for concern. NHS England’s clinical lead for the CDF explained that there would be a great need for extra training to adequately manage the diverse presentations of CRS, given limited existing clinical experience within the NHS.

The committee considered the ERG’s preferred base-case to be most closely aligned with their preferred assumptions, i.e. producing ICERs over £30,000 per QALY gained but less than £50,000. Accordingly, the primary consideration was whether the technology met both criteria to be considered a life-extending treatment at the end of life (EoL) to be eligible for the £50,000 threshold. Though tisagenlecleucel achieved the necessary extension to life (i.e. 3 months), the resolution of the second criterion proved problematic. While the median OS for this patient population was 7.5 months in the von Stackelberg *et al*. 17 study, and 13 weeks in Jeha *et al*.18, it was noted that mean survival in both the company and ERG’s base-case results were significantly longer than the 24 months stipulated in NICE’s EoL criteria. The Committee discussed at length the use of mean over the median OS, which has typically been preferred in previous appraisals. It was argued that the mean did not represent the typical life expectancy of a patient, as this value was driven by a small proportion of long-term survivors who skew mean life expectancy due to their young age and the curative potential of SCT. While this may appear inequitable, as the £50,000 threshold would apply for older patients with similar diseases using mean OS, it was noted that as many more QALYs can be generated by a curative option in young patients, the total cost the NHS is willing to bear is already much higher. The Committee did not consider tisagenlecleucel to meet both of the end-of-life criteria, noting the significant uncertainty associated with the presented survival extrapolations, and what constitutes the current standard of care.

***Cancer Drugs Fund Considerations***

Once the Committee had concluded that the evidence base was not adequate to support a recommendation for routine use, they discussed whether uncertainties around the cost- and clinical-effectiveness could be resolved through further data collection in the CDF. In recognition of the innovative nature of tisagenlecleucel, and the present immaturity of ongoing clinical trials, the committee considered further evidence would be valuable in resolving uncertainties around OS and the technology’s novel mechanism of action. They also considered data collection to offer the opportunity to better understand the costs of subsequent allo-SCT and B-cell aplasia management, and the infrastructural costs of implementation in the NHS. The Committee considered tisagenlecleucel to meet the criteria for use in the CDF for patients who would otherwise receive blinatumomab, and that due to the increasing uptake of blinatumomab and inotuzumab ozogamicin, a judgement against salvage chemotherapy was unnecessary. The Committee therefore recommended tisagenlecleucel for use in the CDF, where it will remain until the conclusion of the ELIANA study (June 2023), at which point NICE’s guidance will be reviewed. The conditions of continued commissioning and patient eligibility criteria can be found in the Managed Access Agreement 7.

The Committee were mindful of statements from clinical experts and NHS England which described the need for new service provision. Infrastructure for transport and storage, staff training and accreditation for administration of the technology, and access to ICUs to manage adverse events such as CRS and acute neurological deterioration need to be considered and carefully planned. In light of this, tisagenlecleucel is undergoing a phased implementation, with a ‘cautious approach’ to treatment planning, particularly concerning the management of adverse events, as these are rare conditions in existing care pathways. It is anticipated that tisagenlecleucel will be fully available across England by April 2020. NHS England has also established a National CAR-T Clinical Panel (NCCP), which will prioritise patients for treatment based on patient need, service capacity, and location to ensure equity of access.

# Conclusions

This appraisal represents an early view of the HTA process for next-generation immunotherapies, and illustrates how current reimbursement frameworks value and incentivise the development of potentially curative technologies.

The uncertainties inherent to the evaluation of such technologies in a rapidly evolving fields presents a number of challenges. The selection of appropriate comparator regimens, and more importantly, suitably mature data relevant to both the target population and current practice is troublesome or even impossible, especially in paediatric oncology where head-to-head trial data is scarce. This is particularly important as the choice of comparator (i.e. what constitutes the standard of care) has ramifications that extend beyond simply the technology’s relative efficacy. The selection of blinatumomab over FLA-IDA determined whether EoL criteria applied, and by extension the value ascribed to the health outcomes produced by tisagenlecleucel. As in many cancer appraisals, the appropriate extrapolation and establishment of longer-term OS was central to the valuation of benefits of tisagenlecleucel. However, the immaturity of available OS data and the technology’s novel mechanism of action impeded reliable estimation of long-term benefits. These uncertainties were a central driver of cost-effectiveness with alternative assumptions producing a wide range of possible ICERs. This was a key factor in the decision to only approve tisagenlecleucel within the CDF, as further data collection is required to determine the appropriateness of survival modelling techniques for characterising the benefits of CAR-T products.

More broadly, a number of relevant issues were raised during this STA, which may impact upon the future appraisal of regenerative medicines. Firstly, the complexity of the care and management requirements for regenerative medicines and cell-based immunotherapies was highlighted, as was the need for increased capacity beyond the limited number of specialist centres capable of administering these technologies. Investments by the NHS in a National CAR-T Clinical Panel (NCCP) will hopefully help bridge this infrastructure gap and expand capacity while ensuring equity of access. Secondly, it highlighted the difficulty of interpreting NICE’s EoL criteria in the context of curative therapies, and the valuation of a cure with high front-loaded costs versus simple extension to life. Current NICE methods guidance is intentionally vague on this subject with intent of allowing Committee discretion based on the issues relevant to an appraisal, but further clarification of NICE’s position on EoL in such situations may be necessary to ensure consistency and equity in decision-making.

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**Author Contributions**

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**Compliance with Ethical Standards**

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**Conflict of interest**

Matthew Walton, Sahar Sharif, Rob Hodgson, Lindsay Claxton, and Mark Simmonds have no conflicts of interest.

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