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Evidence Review Group's Report

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years

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Contributions of authors

Matthew Walton, Rob Hodgson, and Lindsay Claxton wrote the cost effectiveness sections and conducted the ERG economic analyses. Sahar Sharif wrote the clinical effectiveness sections of the report. Rob Hodgson provided advice, commented on drafts of the report and took overall responsibility for the cost effectiveness sections. Kath Wright wrote the sections on the search strategies. Mark Simmonds provided advice, commented on drafts of the report and took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data and academic-in-confidence (AIC) data are redacted.

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List of abbreviations

AEs	Adverse events
ALL	Acute Lymphocytic Leukaemia
BoR	Best overall response
CEA	Cost-effectiveness analysis
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CS	Company submission
CSR	Clinical study report
CLCN	Childhood Leukaemia Clinicians Network
DoR	Duration of remission
EFS	Event-free survival
EMA	European Medicines Agency
ERG	Evidence review group
FAS	Full analysis set
HRQoL	Health related quality of Life
HTA	Health Technology Assessment
SCT	Stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
K-M	Kaplan-Meier
LYS	Life Years
MAIC	Matched adjusted indirect comparison
MRD	Minimal residual disease
MOS	Median overall survival
NICE	National Institute for Health and Care Excellence
NOPHO	Nordic Society of Paediatric Haematology and Oncology
OS	Overall survival
ORR	Overall remission rate
PR	Partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RFS	Relapse-free survival
SAEs	Serious adverse events
SOC	Standard of care

tisagenlecleucel-T	Tisagenlecleucel
TKI	Tyrosine kinase inhibitor
TTO	Time trade off
TYA	Teenager and young adults
WTP	Willingness-to-pay

1   Summary

Acute lymphoblastic leukaemia (ALL) is a rare cancer that affects the blood and bone marrow. It is characterised by an overproduction of immature white blood cells, called lymphoblasts or leukaemic blasts [1]. As an acute cancer ALL progresses rapidly and if left untreated can result in death. It is the most common type of childhood leukaemia, and one of the most common cancers to affect children and young adults. The age group with the highest incidence is young children aged 0-4 years [2]. The two main types of lymphocytes affected are B-cells and T-cells, with B-cell ALL representing 80-85% of cases in children [3].

Long-term survival rates are as high as 90%, however around 15-20% of patients will relapse. Second remission rates remain relatively high at 71-93%, however, the chances of achieving complete remission is substantially reduced with every subsequent relapse, with 55% of these patients relapsing again [4]. A small proportion of patients (2-3%) experience refractory disease, which is defined as a lack of complete remission after chemotherapy treatment [5]. Prognosis is dependent upon a range of factors including age, disease stage and subtype of ALL, however patients with relapsed and refractory B-cell ALL have a particularly poor prognosis [6].

1.1   Critique of the decision problem in the company's submission

The population considered in the company submission (CS) was paediatric and young adult patients up to 25 years of age with relapsed and refractory (r/r) B-cell ALL that are refractory, in relapse post-transplant, or in second or later relapse, which matches the NICE scope. The clinical evidence is also restricted to patients with a life expectancy of 12 weeks or more. The ERG considers that this may result in patients selected onto these trials being generally fitter and healthier than the eligible patient population.

The intervention identified by the NICE scope and the CS is tisagenlecleucel-T (tisagenlecleucel-T). It is currently awaiting EMA marketing authorisation. The intended target dose of tisagenlecleucel-T is 0.2 to 5.0 x 10^6 CAR-positive viable T-cells/kg body weight for patients weighing less than 50 kg. For patients weighing more than 50kg the intended dose is 0.1 to 2.5 x 10^8 CART-positive viable T-cells. The intervention comprises of four stages: leukapheresis, bridging chemotherapy, lymphodepleting chemotherapy, and a single intravenous infusion. The company state the complete process takes 3 weeks. However, the process took 16 weeks in the ELIANA trial, which has considerable implication for eligible patients due to the pace of disease progression and their estimated life expectancy of 3-9 months [7-10].

The comparator specified in the NICE final scope and in the CS is: "Established clinical management without tisagenlecleucel-T at one of the following lines of therapy: second or greater bone marrow relapse; any bone marrow relapse occurring after at least 4 months following allogeneic SCT; primary refractory disease; Ph+ve ALL intolerant to or having failed 2 lines of TKI (tyrosine kinase inhibitor) therapy, or where TKI therapy is contraindicated; PH+ve ALL patients ineligible for allogenic-SCT". The CS considered salvage chemotherapy (FLA-IDA) and blinatumomab to represent the most relevant comparators to tisagenlecleucel for paediatric and young adult patients with r/r B-cell ALL. Clinical advice to the ERG was that blinatumomab is increasingly being used as first line salvage chemotherapy in both paediatric and TYA patients. Therefore, FLA-IDA and FLAG-IDA are regarded as the preferred treatment options.

The CS statement of the decision problem adheres to the clinical outcome measures specified in the NICE scope (overall survival, progression-free survival, response rate, rate of allogenic SCT, adverse effects of treatment and health-related quality of life). Patient-reported outcomes were measured in ELIANA but were not endpoints in ENSIGN or B2101J.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included data from three ongoing, single-arm, phase II, open-label studies: ELIANA, ENSIGN and B2101J. All three trials evaluated tisagenlecleucel-T in paediatric and young adult patients with r/r B-cell ALL. ELIANA is a study of ■ patients. The full intention-to-treat (ITT) population, which includes all enrolled patients, comprised ■ patients. ENSIGN is a study of 58 patients. The full ITT population comprised 73 patients. B2101J is a study of ■ patients. The full ITT population comprised of ■ patients.

For the full ITT population, the EFS and OS rates at 12 months in ELIANA were approximately ■% and ■%, respectively, with a non-estimable median OS. In ENSIGN the probability of EFS and OS at 12 months was approximately ■% and ■%, with a median OS of ■ months. In B2101J the EFS and OS rates at 12 months were approximately ■% and ■%, respectively. The median OS was non-estimable. In addition, the results showed that patients enrolled but not infused with tisagenlecleucel-T have a very poor prognosis.

Patient reported outcomes were only assessed in ELIANA, using the paediatric quality of life questionnaire (PedsQL) and the EQ-5d-3L in patients who had achieved CR/CRi. Only patients aged 8 years or over were included. There were clinically meaningful differences observed between baseline and time points at 6, 12 and 18 months for both the PedsQL and EQ-5d-3L.

The proportion of patients receiving an allo-SCT was high in ELIANA, ENSIGN and B2101J (████%, ████% , ████%, respectively). The KM curves for OS and showed patients in ELIANA and ENSIGN who received an allo-SCT after infusion had a higher rate of overall survival at 6, 12 and 20 months compared to patients who did not have an allo-SCT post infusion. However, EFS for both trials did not differ significantly between the two groups. The CS pooled data from the three tisagenlecleucel-T studies as part of a meta-analysis. The CS reported for patients infused with tisagenlecleucel-T the probability of EFS and OS at two-years was ████% and ████%.

The CS used the von Stackelberg *et al*. (28) as evidence for the comparator treatment blinatumomab. No studies of FLA-IDA were identified, and the CS instead use evidence on clofarabine from Jeha *et al*. (21) as a proxy for salvage chemotherapy (FLA-IDA). The ERG identified a further study as evidence for salvage chemotherapy not reported in the CS. Kuhlen *et al*. (2017), was a retrospective analysis of 242 paediatric patients with r/r B-cell ALL in first relapse post allo-SCT. The 3-year probability of EFS and OS was 15% and 20%, respectively.

The company presented a matched-adjusted treatment comparison (MAIC) with data from the pooled tisagenlecleucel-T population and from the von Stackelberg *et al*. and Jeha *et al*. populations. The hazard ratios show a positive effect of tisagenlecleucel-T compared to both blinatumomab and salvage chemotherapy. However, the MAIC was not able to adjust for all key baseline characteristics and structural differences between trials.

1.3   Summary of the ERG's critique of clinical effectiveness evidence submitted

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 ERG noted some limitations regarding 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. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. In addition, B2101J had a multiple infusion dosing regimen for tisagenlecleucel-T. This may have contributed to improved drug persistence and therefore biased long-term outcomes in B2101J.

The ERG has several concerns with the analyses presented. There is a delay between enrolment and infusion with Tis-T. The evidence submitted in the original CS presented survival curves only from time of infusion, not time of enrolment, thereby excluding any events occurring between these times. The ERG considers that this does not represent results for a true intention-to-treat population, and so overstates the benefits of tisagenlecleucel. The company, on request, supplied survival curves that included all patients enrolled. These showed markedly lower survival rates. The median time

between enrolment and infusion of tisagenlecleucel-T in all three trials was substantially longer than the 3 to 4 weeks estimated in the CS. This has considerable implication for eligible patients due to the pace of disease progression and their short-estimated life expectancy. 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-T.

For all patients enrolled with tisagenlecleucel-T, the ERG notes that the ELIANA KM plots for OS are heavily influenced by censoring of data. In ENSIGN and B2101J the median OS should be interpreted with caution, as there are small numbers of patients at risk beyond 18 and 36 months, respectively. Longer follow up is required to reduce this uncertainty; a 5-year follow up would be a better indicator for considering the curative intent of tisagenlecleucel-T.

The meta-analysis for the tisagenlecleucel-T studies was not for the full ITT population, only for patients who have been infused with tisagenlecleucel-T. The ERG considers it to be essential that the full population intended to receive tisagenlecleucel-T be considered to account for events occurring before time of infusion. Excluding these events will overestimate the survival probabilities when using tisagenlecleucel-T.

There are concerns regarding the comparability of Stackelberg *et al*. and Jeha *et al*. trials to the tisagenlecleucel-T trials, with several differences in study design and baseline characteristics. Therefore, comparing these studies would produce unreliable results. There was insufficient evidence presented to justify using clofarabine as a proxy for FLA-IDA. The ERG does not consider Stackelberg *et al*. or Jeha *et al*. as suitable evidence of the comparators. The much larger sample size and longer follow-up of Kuhlen *et al*. provides a more reliable and robust data set compared to the studies identified by the company.

No head-to-head comparison of tisagenlecleucel with any other treatment was presented. All comparisons were based on adjusted or unadjusted indirect comparisons, which are prone to bias if adjustment is not perfect. The comparisons were placed at further risk of bias because, as noted above, data on tisagenlecleucel was measured from time of infusion, excluding patients who were not infused. The ERG considers this to be an unfair comparison with patients in other trials, who were never considered for infusion, and therefore considers the results of the comparative MAIC analysis to be unreliable.

1.4   Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life, and resource use associated with tisagenlecleucel-T in the treatment of r/r B-cell ALL. The review identified four economic evaluations of tisagenlecleucel-T, including two models that took a UK perspective. These models were based primarily on hypothetical data, and as such should not be used to make judgements about the cost-effectiveness of tisagenlecleucel-T. The company's review also identified two recently published US studies which evaluated the cost-effectiveness of tisagenlecleucel-T in young people (age<25) with r/r ALL. The inevitable differences between the US health care system and the NHS make it difficult to generalise the results of these models.

The CS presented a *de novo* cohort cost-effectiveness model to estimate the cost-effectiveness of tisagenlecleucel-T compared with FLA-IDA and blinatumomab in a population of young people with r/r B-cell ALL. Cost-effectiveness was assessed over a lifetime time horizon of 88 years with a 3.5% discount rate applied to both costs and QALYs.

The model structure applied depends upon whether patients are in the tisagenlecleucel-T arm of the model or receive one of the comparator therapies. This is to account for the time taken to manufacture and deliver tisagenlecleucel-T. For patients in the tisagenlecleucel-T arm, a hybrid modelling approach is taken, combining a decision tree and partitioned survival model structure. The short-term decision tree was used to capture the costs and events prior to the point of tisagenlecleucel-T infusion. For patients receiving either of the comparator therapies, the decision tree phase of the model was dispensed with and survival outcomes are determined using a partitioned survival model. The partitioned survival model used the same structure for all therapies and was based on three health states (event free survival, progressed disease and death).

A central feature of the company's model was the concept of cure, and the assumption that a proportion of patients will achieve long-term remission and survival. The model also included an important additional structural assumption, that patients alive in either the EFS or progressive disease health state at 60 months, will revert to a HRQoL similar to that of the general population and incur only nominal further costs related to their previous condition.

The OS and PFS extrapolations for tisagenlecleucel-T were based on a pooled analysis of the latest available data cuts of the ELIANA (31st December 2017), ENSIGN (6th October 2017), and B2101J trials (30th January 2017). This dataset did not include patients who were enrolled but not infused with tisagenlecleucel-T. To extrapolate the observed OS and EFS data, the company fitted a number of standard parametric models, spline models and mixture-cure models. The model selected for the

company's base-case analysis was a mixture-cure model, wherein the survival of 'uncured' patients is modelled with a single parametric exponential curve and the mortality rate of the fraction of patients considered 'cured' is equal to the age and gender matched general population mortality rate.

Historical control datasets were identified through a systematic review to establish relative effectiveness of tisagenlecleucel-T compared to blinatumomab and FLA-IDA. Overall survival data for blinatumomab was sourced from von Stackelberg *et al.* (2016); a Phase 1/2 trial which evaluated blinatumomab in a paediatric population of patients with relapsed B-cell ALL. No trials were identified evaluating FLA-IDA in a relevant population. Overall survival data for FLA-IDA was therefore derived from Jeha *et al.* (2006) which evaluated clofarabine monotherapy in a mainly paediatric population with r/r B-cell ALL.

A range of approaches were explored to extrapolate the available OS data for the comparators, including standard parametric models, spline models and mixture-cure models. The base-case survival model selected for blinatumomab was a mixture-cure model based on a log-normal function. The base-case survival model selected for FLA-IDA was a standard generalised gamma function, which was used to model survival up to 5 years. After this period patients were assumed to face an age and gender matched general population mortality rate adjusted using a standardised mortality ratio.

The estimates used in the company's base-case analysis for health-related quality of life of patients in the event free survival and progressive disease health states were derived from published literature, with the same health state utilities applied across all treatment groups. After 5 years, all living patients switched to a long-term survival (LTS) health state, with utilities applied also sourced from published literature. To reflect age-related decline in HRQoL, utility values for LTS were adjusted by applying age related decrements over the modelled time horizon.

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. SCT). The cost of allogeneic HSCT included two elements: (i) the initial cost of transplant (cost of the procedure and associated hospitalisation) and (ii) the cost of long-term care post-transplant. The model also included resource and cost estimates for the pre-progression and progression health states based on a previous NICE TA. The same health state costs were assumed for each treatment and hence differences between treatments were determined by differences in the proportion of patients residing in each health state over time. Patient access scheme (PAS) discounts are available for tisagenlecleucel-T, blinatumomab, and the anti-cytokine therapy tocilizumab used to treat cytokine-release syndrome.

The company found tisagenlecleucel-T to be more costly (cost difference of ████████) and more effective (████ QALYs gain) compared with blinatumomab. The deterministic base case ICER was £18,392 per QALY, and the mean probabilistic ICER was £20,046 per QALY. Compared with FLA-IDA, the company found tisagenlecleucel-T to be more costly (cost difference of ████████) and more effective (████QALYs gain). The deterministic base case ICER was £25,404 per QALY, and the mean probabilistic ICER was £27,066 per QALY. These results do not include PAS discounts available for blinatumomab and tocilizumab. The majority of the QALYs gained were generated as a result of additional life years. The company reported that the most influential parameters in the one-way sensitivity analysis included the rate of SCT and utilities applied in the EFS health state.

1.5   Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG highlights that the observed data for tisagenlecleucel-T were collected over a short follow-up when compared with the period of extrapolation over which the majority of the QALY gains are accrued. Furthermore, the plateau in the OS data upon which the company base the assumption of long-term cure is based on very small numbers of patients at risk, and limited experience of CAR-T cell therapies. The ERG notes that the novel mechanism of action means the implications of an ~18 month OS plateau cannot be considered analogous to that following SCT, which has been proven to be curative over several decades. Extrapolation of survival data based on experience with other therapies is therefore subject to additional layers of uncertainty, as the persistence of a long-term CAR-T cell treatment effect is not well characterised. Given this, the ERG considers there to be substantial uncertainty as to how the survival data and associated survival curves will develop over time.

This uncertainty in the extrapolation of the OS data are exemplified in the significant range in predicted cure fraction reported across the alternative mixture cure models for OS (between ████ to ████), and the lack of consistency between the cure fractions reported for OS and EFS. The company's base case used the second most optimistic cure fraction of ████, which the ERG notes is in excess of the observed proportion in long-term EFS of ████, which is not clinically realistic.

The ERG also notes issues in the extrapolation of the available OS data for the comparator therapies. The ERG questions the application of a cure model to blinatumomab, and again notes the uncertainty in cure fraction estimates (3.9 – 21.7%). The ERG also notes the significant difference between the cure fraction selected by the company of 11.4%, and the approximately 21% used in the appraisal of blinatumomab in adults; implying prognosis is significantly better in adults than in paediatric patients, despite a near identical OS KM curve. With respect to salvage chemotherapy, the ERG considered the fitting of a parametric curve to clofarabine OS data inappropriate, given the use of mixture cure

models for the other arms. While cure models were discarded by the company on the grounds of clinical plausibility, the ERG highlights that the estimated cure fractions (7.2 – 9.4%) are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable.

The ERG also does not consider the company to have adequately justified the their selection of Jeha *et al*. (2006) to model the clinical effectiveness of salvage chemotherapy, and does not consider this trial an appropriate basis for informing efficacy estimates for salvage chemotherapy. External evidence sources suggest that the long term survival benefits of blinatumomab relative to salvage chemotherapy are relatively small. The ERG suspects significant prognostic differences between patients recruited to the tisagenlecleucel-T trials, and those recruited to the studies of clofarabine-based regimens considered by the company, which appears to be corroborated by comparison with pre-infusion OS data from ELIANA and ENSIGN.

The ERG also highlights the uncertainty regarding the current treatment of ALL patients with 2+ relapses in the NHS. 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 means this population would not be eligible for blinatumomab again after a second relapse, as considered in this appraisal. Clinical advice to the ERG and company suggests this is also increasingly becoming the case in paediatric patients, the implication being that FLA-IDA may be the most relevant comparator for patients with two or more relapses. The ERG also considers the impact of blinatumomab use earlier in the treatment pathway may raise the issue of eligibility for tisagenlecleucel-T after 2+ relapses. Patients who had previously used an anti-CD19 therapy such as blinatumomab were excluded from all three tisagenlecleucel-T 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. This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy.

1.6   ERG commentary on the robustness of evidence submitted by the company

1.6.1   Strengths

Clinical effectiveness

The clinical effectiveness was derived from two directly relevant, good quality RCT's, ELIANA and ENSIGN, with B2101J also being relevant. The results of these trials provide reliable evidence of overall survival and event-free survival in r/r B-cell ALL patients treated with tisagenlecleucel-T; the pooled median survival is ▮▮▮▮▮▮▮▮.

Cost effectiveness

The ERG considered the company's economic submission to meet the requirements of the NICE reference case and captured a number of clinical elements of the treatment of r/r B-cell ALL. The company's analysis also presented an extensive range of scenario analyses which were further supplemented by evidence and analyses provided in response to the ERG's points for clarification.

1.6.2 Weaknesses
Clinical effectiveness

The lack of head-to-head data is a considerable weakness when evaluating tisagenlecleucel-T. The chosen comparator studies (von Stackelberg *et al*. and Jeha *et al*.) are substantially different in design and characteristics, and are of poor quality when compared to the tisagenlecleucel-T studies. It is unclear whether these represent reasonable comparisons to tisagenlecleucel-T and whether survival data extracted from them is reliable. There is considerable uncertainty as to whether blinatumomab is an appropriate comparator and whether using clofarabine is a reasonable proxy for salvage chemotherapy. Longer follow-up is required to consider the curative intent of tisagenlecleucel-T.

Cost effectiveness

The ERG considers that are a number of important areas of uncertainty with regards the clinical data available to support the project benefits of tisagenlecleucel-T. Specifically, the ERG notes the following:

1) *All the estimates of comparative effectiveness in the CS are based on non-randomised comparisons with limited adjustment for confounding.*

A significant area of uncertainty regarding the comparative effectiveness of tisagenlecleucel-T is the use of historical control data to establish the effectiveness of the comparator therapies FLA-IDA and blinatumomab. In particular concerns were raised regarding the comparability of the populations recruited to the three tisagenlecleucel-T trials and the comparator trials, and notes differences in key baseline characteristics and as well as structural differences between trials.

2) *OS data is immature for tisagenlecleucel*

Significant uncertainties remain regarding the extrapolated OS estimates for tisagenlecleucel-T and the use of a mixture cure modelling approach, given the immaturity of current evidence. As highlighted above, data was collected over a short follow-up period relative to the extrapolation over

which the majority of the QALY gains are accrued, this is important as small changes in projected OS can have a significant impact upon the long-term benefits.

3) *The evidence source used for the comparator regimens and the uncontrolled nature of the comparisons*

The ERG considers the main source of uncertainty in relation to the OS estimates for the comparator regimens to be the use of Jeha *et al*. (2016) in the company's base-case. The ERG does not consider this study to provide an appropriate basis for informing OS estimates for the population who would be eligible for treatment with tisagenlecleucel-T. The ERG identified two recently published studies on patients with r/r ALL; Sun *et al*. (2018)[4] and Kuhlen *et al*. (2017) [12]. These may be a more appropriate source of comparator data for patients on salvage chemotherapy, as they provide data on a substantially larger sample of patients with more mature survival data.

4) *Uncertainty surrounding broader infrastructure and training requirements*

Given the complexity of this intervention and patient care needs, the lack of a clear service specification for the production, provision, and administration of tisagenlecleucel-T on the NHS, the ERG considers there to be important remaining uncertainties regarding the quantification of additional required resource and investment for implementation of tisagenlecleucel-T on the NHS. Particular consideration should be given to additional infrastructure requirements that have not been captured in the presented analyses. The ERG highlight particular uncertainty surrounding additional paediatric ICU capacity which may need to be made available (even if not used) to ensure that patients receiving tisagenlecleucel-T can be guaranteed access to appropriate services if and when required, without adversely affecting the provision of care to other patients.

5) *Uncertainties surrounding adverse events*

Considerable uncertainty exists regarding any long-term adverse effects of tisagenlecleucel-T. In particular, the ERG notes uncertainty regarding the duration of B-cell aplasia, which potentially requires ongoing treatment with intravenous immunoglobulin (IVIG).

1.7   Summary of exploratory and sensitivity analyses undertaken by the ERG

The key uncertainties addressed by the ERG scenario analyses relate to the:

- Assumptions made regarding the around the OS and costs associated with non-infused patients in the tisagenlecleucel-T arm of the model
- Methods used to analyse extrapolate OS data,

- The source of clinical data used to estimate the survival of patients on salvage chemotherapy

- The duration of B-cell aplasia duration and costs of IVIG,

- Post-SCT quality of life and anticipated SCT uptake in practice,

- Number of lines of blinatumomab treatment modelled,

- The health state utilities used in the model.

The results of these scenario analyses including the ERG's base-case are summarised in Table 1. Due to time constraints, deterministic ICERs are presented throughout, with the exception of the ERG alternative base-case, which is based on the probabilistic analysis.

Table 1 Results of corrections and relevant scenarios included in the ERG's base-case analysis (includes tisagenlecleucel-T PAS)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER	ΔICER from CBC
Company's base-case results						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,404	-
Blinatumomab	███	███	███	███	£18,392	-
1. Company's base-case results including ERG's mortality calculation correction						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£28,806	£3,402
Blinatumomab	███	███	███	███	£20,864	£2,471
2. Salvage chemotherapy OS and EFS data from Kuhlen et al. 2017. Mixture cure model (OS lognormal, EFS lognormal)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£33,110	£7,706
Blinatumomab	███	███	███	███	£18,147	-£245
3. Blinatumomab OS log-logistic mixture cure model (EFS based on OS)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,368	-£36
Blinatumomab	███	███	███	███	£19,051	£659
4. Tisagenlecleucel-T OS log-logistic mixture cure model (EFS gen. gamma)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£28,203	£2,798
Blinatumomab	███	███	███	███	£21,284	£2,891
5. Tisagenlecleucel-T ELIANA EFS & PD utilities, LTS from Kelly et al. (>2 years)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,808	£404
Blinatumomab	███	███	███	███	£18,796	£404
6. Lower disutility applied from 3 – 12 months post-SCT						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,403	-£1

Blinatumomab	■	■	■	■	£18,572	£179
7. Non-infused patients independently modelled (Pooled ELIANA & ENSIGN OS)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£25,371	-£33
Blinatumomab	■	■	■	■	£18,108	-£285
8. IVIG used only in patients with hypogammaglobulinaemia (11.4 month duration)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£24,359	-£1,046
Blinatumomab	■	■	■	■	£16,956	-£1,436
9. Patients receive only 2 cycles of blinatumomab						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£25,330	-£75
Blinatumomab	■	■	■	■	£20,196	£1,803
10. Cost of holding ICU beds during CRS risk period included						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£26,382	£978
Blinatumomab	■	■	■	■	£19,735	£1,342
ERG deterministic base-case (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£45,397	£19,992
Blinatumomab	■	■	■	■	£27,732	£9,339
ERG probabilistic base-case (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£48,265	£22,861
Blinatumomab	■	■	■	■	£29,501	£11,109
Key: CBC, company's base-case; HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; MCM, mixture-cure model; PAS, patient access scheme; QALYs, quality-adjusted life year						

The ERG alternative base-case, based on a probabilistic analysis estimated tisagenlecleucel-T to be more costly (cost difference ■ and more effective (■ QALY gain) versus salvage chemotherapy, and more costly (cost difference ■ and more effective (■ total QALY gain) than blinatumomab. The ERG alternative base-case, based on probabilistic analysis, suggests

that the ICER for tisagenlecleucel-T compared with salvage therapy is £48,265 per QALY, and compared with blinatumomab is £29,501.

A further series of deterministic exploratory analyses were conducted on the ERG base-case to explore uncertainties regarding the uptake of SCT in patients receiving and the duration of IVIG use. Both of these issues were found to have significant impact on the estimated ICER and suggest that the most plausible ICER is likely to be between £41,274 per QALY and £65,229 per QALY.

2   Background

2.1   Critique of company's description of underlying health problem.

The ERG summarises the company's description of the health problem as follows:

Relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) is a cancer that affects the blood and bone marrow. It is characterised by an overproduction of immature white blood cells, called lymphoblasts or leukaemic blasts [13]. These abnormal cells build up in the blood and can spread to other parts of the body including the lymph nodes, liver, spleen and the central nervous system [14]. ALL is an aggressive disease that develops rapidly and if left untreated can result in death [15]. Symptoms include anaemia, bone and joint pain, bruising, recurrent infections and swollen lymph nodes [16].

ALL is a rare disease, with around 810 new cases of ALL diagnosed each year in the UK [17]. ALL is categorised according to the type of lymphocyte affected (B or T-cell). B-cell ALL represents the majority of ALL cases in children, around 80-85% [1]. B-cell ALL can further be categorised by the presence of the Philadelphia (ph) chromosome (Ph -ve and Ph +ve patients). Most ALL patients are Ph -ve, with only around 3% of patients having Ph +ve ALL.

The incidence of B-cell ALL is strongly related to age and primarily affects children and young adults, with the highest incidence in children aged 0-4 years old [18]. The disease is the most common form of childhood leukaemia and accounts for 25% of all childhood cancers [1]. Around 80-85% of paediatric and young adult patients will achieve complete remission after first-line chemotherapy, with the proportion of patients surviving at five years approaching 90% in many developed countries [19, 20]. Despite these high remission rates, approximately 15-20% of patients will subsequently relapse [16]. Second remission rates remain relatively high at 71-93%, however, the chances of achieving complete remission is substantially reduced with every subsequent relapse, with 55% of these patients relapsing again[4]. A very small proportion of patients (2-3%) experience primary refractory disease and these patients are typically harder to treat [5]. Clinical advice to the ERG is that although primary refractory patients have poor survival rates, current chemotherapy-based treatments such as the NOPHO-protocol are becoming increasingly effective in treating these patients [21].

The CS states that median overall survival (OS) with current treatment in the relapsed or refractory (r/r) setting ranges from less than 3 months to 7.5 months. However, the ERG notes that there is a wider range of 3.5 months to 9 months reported in Table 19 of the CS[7, 9, 10, 22-24]. In addition, the ERG considers median survival a poor measure of prognosis in ALL because some patients achieve cure. Long-term survival rates for all B-cell ALL patients are reported to be 40% to 50% [5, 6]. Kuhlen *et al*.

reported a long-term survival rate of 21.5%, however this included T-cell ALL patients who tend to have a poorer prognosis than B-cell ALL patients.

The CS does not report important prognostic factors for r/r B-cell ALL patients. Clinical advice to the ERG is that the most significant prognostic factors are age, white blood cell count at diagnosis, number of previous relapses, the Karnofsky/Lanksy performance status and time to first relapse.

Overall, the ERG considers that the CS generally presented appropriate and relevant information on the underlying health problem. However, the CS slightly understated overall survival of r/r B-cell ALL patients on current treatment.

2.2   Critique of company's overview of current service provision

2.2.1   Treatment pathway

The CS stated that there are no paediatric or young-adult specific national clinical guidelines for the treatment of ALL in the UK. However, clinical advice to the ERG is that there are guidelines (albeit unpublished) by the CLCN. Overall, there are limited options for treating r/r B-cell ALL patients and there has been little change in the last decade.

The main aim of treatment for newly diagnosed patients with B-cell ALL is to induce complete remission [25]. Clinical advice to the ERG is that for B-cell ALL patients in second or greater relapse the main aim is bridging to an allogenic stem cell transplant (allo-SCT). Allo-SCT is typically used for high-risk patients who do not respond to chemotherapy treatment. It is also used as consolidation for patients who have relapsed and require additional support after achieving remission [26]. If a patient has already received an allo-SCT treatment options are limited, palliative care and clinical trials are sometimes the only remaining choices.

The current treatment pathway r/r B-cell ALL patients is split into 2 groups: patients less than 18 years old and teenage and young adult (TYA) patients above 18 years old. TYA patients have poorer outcomes compared to patients under 18 years old and tend to have greater treatment resistance. However, TYA patients are increasingly being treated with paediatric protocols, which improve survival outcomes and are therefore, considered separately from adults [27].

First line treatment for both paediatric and TYA patients consists of multi-drug chemotherapy, which typically includes a combination of cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine [28]. Figure 1 Clinical pathway of care for patients with B-cell ALL and potential positioning of tisagenlecleucel-T (Figure 6 of the CS) in the CS shows that patients under 18 years old after first relapse follow the ALLR3 protocol, which is an international collaborative

clinical trial protocol [29]. Whereas, TYA patients are typically treated with blinatumomab. However, on page 25 the CS states that many patients are in fact treated with blinatumomab following a first relapse, which corresponds to clinical advice received by the ERG. The treatment pathway in Table 1 shows patients who experience a second relapse after maintenance therapy, either before or after receiving an allo-SCT are typically treated with either clofarabine, salvage chemotherapy (mainly consisting of FLA-IDA) or blinatumomab depending on first-line salvage therapy used. The CS (p.25) states that the preferred treatment option as this stage is salvage chemotherapy (FLA-IDA), due to blinatumomab being used earlier on in the pathway. Clofarabine is rarely used in the UK due to its toxicity. This was confirmed by the ERG's clinical advisor.

The CS outlines that patients who are primary refractory are severely limited in their options for successful treatment and would typically be treated with either salvage chemotherapy or blinatumomab. However, clinical advice to the ERG suggests that paediatric (<18 years of age) primary refractory patients are usually treated using the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol, which treats patients based on risk-group stratification for remission induction therapy[30]. The NOPHO protocol has shown substantial improvements in survival for primary patients [21]. TYA primary refractory patients are not typically treated with the NOPHO protocol; rather clinical advice is that they tend to receive blinatumomab. However, there are no specific guidelines for these patients.

The company's overview of current service provision is therefore generally appropriate and relevant to the decision problem; however, the CS did not include the NOPHO protocol treatment option for primary refractory patients. The typical treatment pathway for r/r B-cell ALL patients, with the anticipated place of tisagenleuclecel (tisagenlecleucel-T) within the pathway, is presented in Figure 1. Tisagenlecleucel-T is positioned as a treatment option for primary refractory, in relapse post-transplant, or in second or later relapse patients. However, due to current treatment being highly effective for primary refractory patients, clinical advice to the ERG is that these patients would be less likely to receive tisagenlecleucel-T. Rather, tisagenlecleucel-T would be used as treatment for patients further along the pathway.

Figure 1 Clinical pathway of care for patients with B-cell ALL and potential positioning of tisagenlecleucel-T (Figure 6 of the CS)
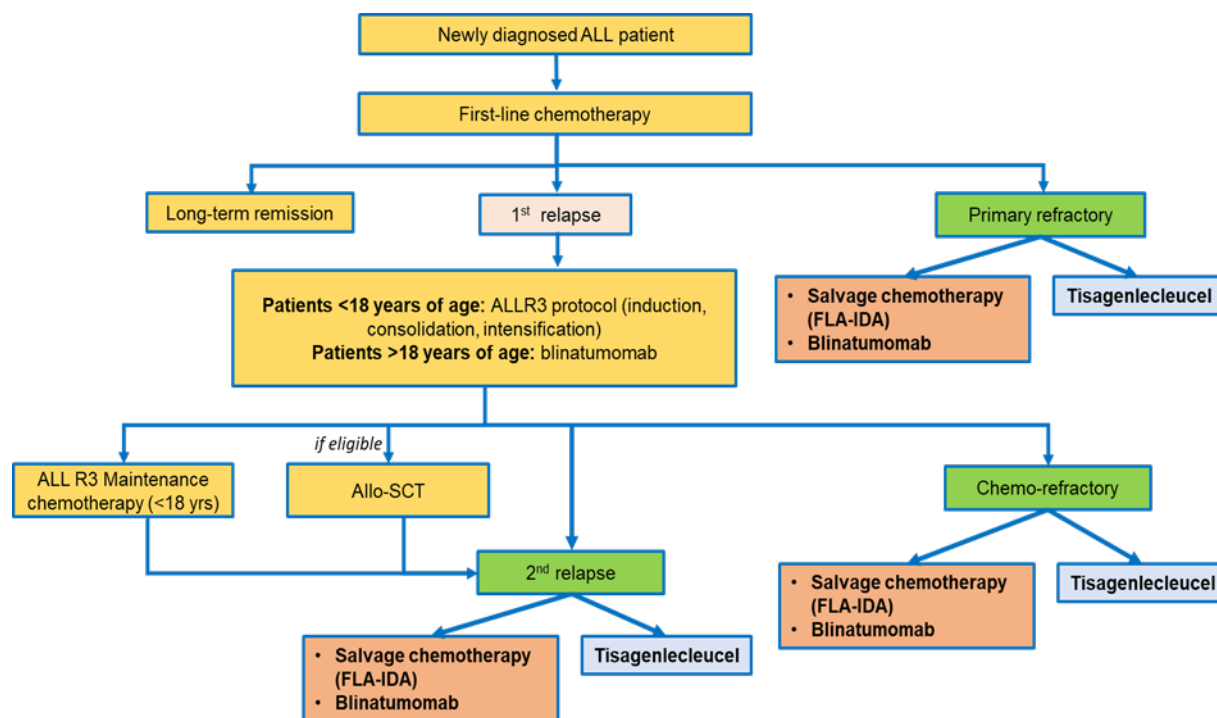
Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: stem cell transplantation; FLA-IDA: fludarabine, cytarabine and idarubicin.

3   Critique of company's definition of decision problem

3.1   Population

The CS provides an overview of the decision problem (p12) and defines the target population, in line with the final scope, as:

"Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that are refractory, in relapse post-transplant, or in second or later relapse." The clinical evidence presented is primarily from three single-arm trials: ELIANA, ENSIGN and B2101J. The populations generally match that defined in the decision problem, but there are some differences. The final scope issued by NICE is indicated for patients aged 3 to 25 years old. Both the ELIANA and ENSIGN trials exclude patients less than 3 years old, which matches the scope. However, the CS reports that the anticipated license for tisagenlecleucel-T is for patients aged 0-25 years old. Patients under three years old account for a significant proportion of the licensed population [2]. The incidence of ALL among children aged 2 to 3 years old is approximately fourfold to fivefold greater than that for children aged 10 years and older[31]. While it is uncertain whether this also reflects patients with r/r

disease, the ERG considers that the trial populations may not fully reflect the characteristics of the eligible NHS population.

The ELIANA, ENSIGN and B2101J trials are restricted to patients with a life expectancy of 12 weeks or more. The ERG considers that this may result in patients selected onto these trials being generally fitter and healthier as the median overall survival (OS) for r/r B-cell ALL patients on current treatment such as salvage chemotherapy is approximately 13 weeks, as reported in the CS. However, the ERG acknowledges that current chemotherapy-based treatment may be more toxic than tisagenlecleucel-T. Clinical advice to the ERG is that although this might exclude some of the eligible patient population, in practice, patients who are extremely ill would be treated with standard chemotherapy-based salvage treatment rather than tisagenlecleucel-T. Also, as there is a delay of several weeks between being assigned tisagenlecleucel-T and receiving infusion, restricting tisagenlecleucel-T to patients likely to survive this waiting period is reasonable.

The populations considered in the ELIANA, ENSIGN and B2101J may be broader than expected in NHS practice, due to the inclusion of primary refractory patients. The ERG is unsure whether primary refractory patients would be treated with tisagenlecleucel-T in practice. Clinical advice to the ERG highlighted that current treatment, such as the NOPHO protocol, has been shown to be effective in these patients and thus, tisagenlecleucel-T is less likely to be adopted[30]. However, the number of primary-refractory patients in these trials was small: ██%, ██% and ██%, respectively.

Evidence for the comparator treatments come from the von Stackelberg *et al*. trial [8] and the Jeha *et al* trial [7]. Both studies poorly reported baseline characteristics including genetic abnormalities and primary refractory status, which restricts the ability to ascertain how reflective the patients are of clinical practice. The populations in these trials also differed from the population defined in the decision problem. Both trials have a younger patient population. Von Stackelberg *et al*. excludes patients above 18 years old and Jeha *et al*. excludes patients above 21 years old. Whereas, the NICE scope defines the target population as 0 to 25 years old [32]. von Stackelberg *et al*. includes patients in first relapse (after full salvage induction regimen). The ERG highlights that patients in their first relapse would not receive tisagenlecleucel-T in clinical practice, they also tend to have a better prognosis than patients in second or greater relapse [6]. Therefore, both the comparator trial populations do not fully represent the eligible NHS population.

3.2 Intervention

The intervention was as specified in the final scope as tisagenlecleucel-T (tisagenlecleucel-T). The company describe tisagenlecleucel-T as a single-dose, immunocellular gene-transfer therapy. It is

currently awaiting EMA marketing authorisation. CHMP approval was expected in ▮▮▮▮▮▮. In 2017 it received regulatory approval from the Food and Drug Administration in the US[33].

The intended target dose of tisagenlecleucel-T is 0.2 to 5.0 x 10^6 CAR-positive viable T-cells/kg body weight for patients weighing less than 50 kg. For patients weighing more than 50kg the intended dose is 0.1 to 2.5 x 10^8 CART-positive viable T-cells (non-weight based). The intervention comprises of four stages: leukapheresis, bridging chemotherapy, lymphodepleting chemotherapy, and a single intravenous infusion. Prior to manufacture patients undergo leukapheresis to collect white blood cells; these are then shipped to the manufacturer to engineer T cells with CAR. The patient can receive bridging chemotherapy between leukapheresis and tisagenlecleucel-T infusion. Prior to infusion, the patients receive a low dose lymphodepleting regimen, which consists of fludarabine and cytarabine. Delivery of tisagenlecleucel-T is anticipated to require specialist centres, with patients needing prolonged observation and access to emergency care in the event of side effects. The company state the complete process takes 3 weeks. However, the process took 16 weeks in the ELIANA trial, which has considerable implication for eligible patients due to the pace of disease progression and their estimated life expectancy of 3-9 months [7-10].

The company propose that tisagenlecleucel-T is an end of life and curative treatment, given that the eligible population would otherwise have the option of palliative care or entry into a clinical trial. However, the evidence submitted does not have the long-term follow-up needed to support the claim of being curative. Further discussion regarding evidence supporting tisagenlecleucel-T as an end-of-life therapy can be found in section 7.

3.3   Comparators

The comparator in the final scope issued by NICE was established clinical management without tisagenlecleucel-T at one of the following lines of therapy:

- second or greater bone marrow relapse;
- any bone marrow relapse occurring after at least 4 months following allogeneic SCT;
- primary refractory disease;
- Ph+ve ALL intolerant to or having failed 2 lines of TKI (tyrosine kinase inhibitor) therapy, or where TKI therapy is contraindicated;
- PH+ve ALL patients ineligible for allogenic-SCT.

The CS considered the relevant comparators to be salvage chemotherapy, specifically FLA-IDA for paediatric patients and FLAG-IDA for TYA patients or blinatumomab [11]. FLA-IDA consists of a

fluorinated purine analog (FL), high-dose cytarabine and idarubicin (IDA). Clinical advice to the ERG agreed that these were the main comparators for the relevant population. The CS reports that blinatumomab is principally used earlier on in the treatment pathway with the aim of bridging to allogenic SCT. Clinical advice confirmed that blinatumomab is increasingly being used as first line salvage chemotherapy in both paediatric and TYA patients. Therefore, FLA-IDA and FLAG-IDA are regarded as the preferred treatment options.

The CS also excluded clofarabine as a comparator due to its toxicity level and hence its rare use in the UK. Clinical advice to the ERG agreed that clofarabine is not a suitable comparator. However, due to a lack of data on FLA-IDA, the CS uses clofarabine monotherapy efficacy data as a proxy for FLA-IDA. The ERG is uncertain about the validity of this proxy given that clofarabine is rarely used in the UK and there are concerns regarding its toxicity. The CS also excluded TKIs on the basis that the proportion of patients with Ph+ve ALL within the eligible patient population would constitute a small minority (<3%) [5].

3.4   Outcomes

The outcomes in the NICE scope that were considered in the CS were; overall survival, progression-free survival, response rate, rate of allogenic SCT, adverse effects of treatment and health-related quality of life.

The primary outcome in the submitted evidence was overall remission rate (ORR) defined as best overall survival (BOR) of either complete remission (CR) or complete remission with incomplete blood count recovery (CRi) determined by independent review committee (IRC) assessment. Secondary outcomes were ORR with minimal residual disease (MRD) negative bone marrow, duration of remission (DoR), event-free survival (EFS) and overall survival (OS). MRD negative status was defined as MRD < 0.01% [34]. Clinical advice to the ERG is that different centres use different thresholds. A higher threshold of 0.001% is commonly used and thus, the lower threshold used in the ELIANA, ENSIGN and B2101J trials may overestimate the proportion of patients that would be considered to have achieved remission (either CR or Cri) in clinical practice.

Patient reported outcomes were measured in ELIANA but were not endpoints in ENSIGN or B2101J. Only patients older than 8 years old were assessed for patient reported outcomes. Thus, except the patient reported outcomes, which were missing from ENSIGN and B2010J, the outcomes specified in the CS decision problem matched the outcomes listed in the NICE scope.

3.5   Other relevant factors

The CS stated that no equality issues related to the use of tisagenlecleucel-T have been identified or are foreseen.

4 Clinical Effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The ERG considers the literature searches to be generally appropriate and likely to have captured all the relevant records but has several comments as follows.

Reporting

The databases used for the effectiveness review are reported as being MEDLINE and MEDLINE in Process (using the PubMED interface), Embase (using the embase.com interface), and the CENTRAL Register (using the Cochrane Library). This is reported in section D.1.1.1 Search Strategy section of the company submission.

The search strategies used in each of the 3 databases are fully reproduced on pages 14-17 of Appendix D and the date that they were conducted is given. The numbers of records retrieved matches the number given in the PRISMA diagram provided on page 21.

There are some inconsistencies in the description of the search strategies between the descriptions provided in the text and the headings used in the tables. In the text (page 13) it is stated that Embase was searched via Embase.com with MEDLINE and MEDLINE In-Process searched via PubMed. However, the headings of Table 2 (page 14) and Table 3 (page 15) suggest that Embase and MEDLINE databases were searched together with MEDLINE In Process searched separately using the PubMED interface.

Additional searches of conference websites were conducted to identify potentially relevant posters and abstracts and the reference lists of identified studies were reviewed.

Searches of the trials registers ClinicalTrials.gov, European Union Clinical Trials Register and the WHO ICTRP were also conducted to find ongoing studies although nothing is reported about the search terms used or which register search identified additional studies.

Strategy

The strategy used in MEDLINE, MEDLINE in Process and Embase consists of sections for the indication, population and treatment further combined with a set of search terms for children. The overall structure of the strategy seems to be appropriate and there are no errors in how the sets are combined. Neither are there any typographical errors within the search terms used.

In both MEDLINE and Embase the search terms for infants/children are restricted to free text terms and do not include any of the available thesaurus terms. By using this approach, it is possible that relevant papers could have been excluded from the results.

A search for grey literature is reported (at end of D.1.1.1) but no information is given about what the search terms were and what they identified by doing these searches.

4.1.2 Inclusion criteria

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was presented as Figure 1 in the CS Appendix, Section D1.3. Ultimately, 66 studies were included within the systematic literature review. A list of these studies is included in Table 7 of the SLR.

Of the 66 studies ultimately identified, seven publications reporting on three clinical trials were selected for tisagenlecleucel-T and two publications reporting on two clinical trials were identified that investigated the use of blinatumomab in paediatric patients with r/r B-cell ALL.

No publications were identified for FLA-IDA in paediatric patients with r/r B-cell ALL. Therefore, an assessment of the included studies was performed to identify efficacy data that could be used as a proxy for FLA-IDA. The CS reports that the 66 studies included in the SLR were systematically assessed based on comparability to the tisagenlecleucel-T trials. They were assessed on population comparability and the availability of relevant EFS and OS measures reported as Kaplan-Meier curves. Studies conducted in Japan and studies evaluating blinatumomab were also excluded. This resulted in 6 studies being selected as proxy for the efficacy of FLA-IDA, reported in Table 19 of the CS (page 69). However, the company then excluded 2 trials with a median OS of 9 months on the basis that the overall survival with FLA-IDA would be 3 months. The ERG does not agree with the exclusion of these trials, given that there is no clinical evidence on OS with FLA-IDA.

The remaining four studies investigated the use of clofarabine combination and monotherapy. The clofarabine combination therapy studies were excluded on the basis that only clofarabine monotherapy is licensed in the UK for paediatric patients. Additionally, the CS states that the clofarabine monotherapy study was most appropriate as the data were used as part of the NICE mock appraisal. The ERG considers these reasons unjustified and unwarranted. It would be more reliable and robust to include all four trials rather than one clofarabine monotherapy trial as a proxy for the efficacy of FLA-IDA.

The CS reports that a conventional indirect treatment comparison was not possible; however, the use of a MAIC approach was explored as part of a scenario analysis. The reason for exclusion from the MAIC is provided for each study in the final column of Table 7 in the CS Appendix

4.1.3   Critique of data extraction
The CS reported that data from the included studies were extracted into Microsoft Excel by one researcher familiar with the subject area and validated by a second, independent researcher. The ERG considers that the methods of data extraction reported are appropriate.

4.1.4   Quality assessment
The quality assessment of the studies identified for inclusion in the systematic review of effectiveness is reported in CS section B.2.5 and Appendix Sections D.1.8. The Good Research for Comparative Effectiveness (GRACE) checklist was used in which 11 questions were answered Yes, No or Not applicable. Six items evaluate the quality of the data, and five items address the methods used in study design and analysis [35].

The GRACE quality assessment checklist has several limitations. No information is provided to support or justify how decisions were made to answer the questions; such information adds transparency to this stage in any systematic review. No insight was provided in the CS regarding how to arrive at an overall judgement on quality or bias; the CS simply stated on p45 that 'all three trials (ENSIGN, ELIANA and B2101J) can be considered to be of good quality', without describing how this judgement was arrived at. No overall judgement was provided for the von Stackelberg *et al*. or Jeha *et al*. studies. The CS did not report the relative importance of the implications of negative answers. No details were provided about how many researchers were involved in the quality assessment process, therefore the possibility of bias affecting the assessments cannot be ruled out.

4.1.5   Evidence synthesis
The CS pooled data from the three tisagenlecleucel-T studies (ENSIGN, ELIANA and B2101J) as part of a meta-analysis. This was done to increase the overall available sample size and to allow the use of the longest-term follow up data available. The CS assessed the feasibility of pooling all three trials by comparing the study design, definition of outcomes and patient baseline characteristics. Although, the definitions of EFS and OS, the main outcome measures informing the economic analysis, were identical across all three studies there were a few differences in study design and baseline characteristics. These are detailed further in section 4.2.2.

4.2   Critique of trials of tisagenlecleucel-T

4.2.1   Tisagenlecleucel-T studies

The CS efficacy analyses were based on three studies: ELIANA, ENSIGN and B2101J. These are single-arm, open-label studies evaluating tisagenlecleucel-T in paediatric and young adult patients with r/r B-cell ALL. The properties of each trial were reported in the CS in Table 4, page 33.

The ERG noted some limitations and concerns about 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. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. The ERG is unsure whether primary refractory patients would be treated with tisagenlecleucel-T in practice, given that clinical advice to the ERG highlighted that current treatment is effective in these patients [30]. Therefore, the populations in all three studies may be broader and healthier than expected in NHS practice.

The ERG also notes that the CS provided baseline characteristics for patients infused with tisagenlecleucel-T rather than the full ITT population enrolled in the trials. The ERG requested baseline characteristics of all patients enrolled in ELIANA, ENSIGN and B2101J, which are presented in the Appendix, Table 31 Patient baseline characteristics for the full ITT population in ELIANA, ENSIGN and B2101J. A comparison of the baseline characteristics shows numerous small differences. The median age in the full ITT population of ENSIGN is higher than in the infused-only population in (██ years vs 12 years, respectively). The proportion of primary refractory patients was larger in the B2101J full ITT population compared to the B2101J infused-only population (██% vs ██%, respectively). There were fewer patients with a Karnofsky performance score of 100 in the full ITT populations compared to the infused-only populations of all three trials.

The CS reported that there was a difference in dosing regimen. Patients in ENSIGN and ELIANA received a single infusion of tisagenlecleucel-T, whereas patients in B2101J received dose escalation treatment with a wider dose range. The ERG identified differences in baseline characteristics between the three trials. This included differences in Karnofsky performance and numbers of patients who had not had a previous SCT.

The ERG recognises an important feature of the technology is that it requires manufacturing, which results in a delay between enrolment and infusion with tisagenlecleucel-T. Therefore, the ERG requested the average median time between enrolment and infusion of tisagenlecleucel-T for the

ENSIGN and B2101J trials, as this was only reported in the CS for ELIANA. The median time between enrolment and infusion of tisagenlecleucel-T in ELIANA, ENSIGN and B2101J was � days, 41 days and ███ days. This is substantially longer than the 3 to 4 weeks estimated in the CS. The ERG requested clarification regarding this discrepancy in the points of clarification. The company described the reasons as follows: demand outweighed capacity at the beginning of the ELIANA trial, as there were fewer manufacturing slots available to produce tisagenlecleucel-T; and there was potential for delays between leukapheresis and the start of manufacturing. The company stated that several incremental changes to the manufacturing process have been implemented to help standardise and streamline the production. This should in turn decrease the time from cell product harvest to release. The company also highlight that recent data published on the throughput time for a total of 37 commercial patient orders for tisagenlecleucel-T report a median time of 23 days (range 21-37 days)[36]. Although, these data correspond to the pre-specified manufacturing time of 3-4 weeks, the range exceeds this. The ERG is concerned that in practice the manufacturing time of tisagenlecleucel-T may take significantly longer than 3-4 weeks, which has considerable implication for eligible patients due to the pace of disease progression and their estimated life expectancy of 3 to 9 months.

Additionally, the ERG notes that tisagenlecleucel-T trials excluded patients who had previously been treated with an anti-CD19 therapy such as blinatumomab. Given the use of blinatumomab earlier on in the treatment pathway, this may raise the issue of eligibility for tisagenlecleucel-T on the NHS, as many patients treated with blinatumomab experience CD-19 negative relapse. There is also uncertainty regarding the effectiveness of tisagenlecleucel-T following blinatumomab rather than chemotherapy-based salvage therapies.

The outcomes used in the cost-effectiveness modelling were overall survival and event-free survival. Table 2 below summarises the results for these outcomes for all three trials. The ERG highlights that the results in Table 2 are not based on the full ITT population; they do not include patients enrolled but not infused with tisagenlecleucel-T.

Table 2 Summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J (adapted from Table 11 of the CS on page 47)

	ELIANA (N=▮) (N=▮ for ORR)	ENSIGN (N=58) (N=42 for ORR)	B2101J (N=▮)
ORR (CR+CRi) (95% CI; p value)	▮▮▮▮▮▮	29 (69.0) (52.9, 82.4; <0.0001*)	▮▮▮▮▮
EFS			
% event free at 6 months (95% CI)	▮▮▮▮	▮▮▮▮	▮▮▮▮
% event free at 12 months (95% CI)	▮▮▮▮	▮▮▮▮	▮▮▮▮
Median (months) (95% CI)	▮▮▮	▮▮▮	▮▮▮
OS			
% at 6 months (95% CI)	▮▮▮▮	79.3 (64.9, 88.4)	▮▮▮▮
% at 12 months (95% CI)	▮▮▮▮	62.6 (45.8, 75.6)	▮▮▮▮
Median (months) (95% CI)	▮	23.8 (8.8, NE)	▮▮▮▮

* No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented.

Key: NE: not estimable, CI: confidence interval, EFS: event-free survival, OS: overall survival, ORR: overall remission rate, CR: complete remission, CRi: complete remission with incomplete blood count recovery

4.2.1.1 Key properties of ELIANA

ELIANA was an ongoing phase II, multicentre, single-arm, open-label study that is evaluating tisagenlecleucel-T in ▮ patients with r/r B-cell ALL. The full intention-to-treat (ITT) population, which includes all enrolled patients, comprised ▮ patients. The company provided reasons for exclusion following screening in the points for clarification response. Basic details of the different analysis data-sets are presented in Table 8 of the CS (p42), which includes the cohorts: the 'full analysis' set (n=▮) and the efficacy analysis set (n=▮). The full analysis set only includes patients who were infused with tisagenlecleucel-T, and the efficacy analysis set only includes patients for whom there is at least 3 months between infusion and the data cut off (31st December 2017), which was used for the ORR and DoR outcomes. The ERG requested data on the full ITT population (all patients enrolled in the trial). The company provided baseline characteristics for the full ITT population in the points of clarification response (Appendix, Table 31 Patient baseline characteristics for the full ITT population in ELIANA, ENSIGN and B2101J). Clinical advice to the ERG was that the ELIANA population is broadly generalisable to the NHS r/r B-cell ALL patients.

4.2.1.2 Key properties of ENSIGN

ENSIGN is an ongoing phase II, multicentre, single-arm, open-label study that is evaluating tisagenlecleucel-T in 58 patients with r/r B-cell ALL. The full ITT population, which includes all enrolled patients, comprised 73 patients. The company provided reasons for exclusion following screening in the points for clarification response. Basic details of the different analysis datasets are presented in Table 8 of the CS (p42), which includes the cohorts: the 'full analysis' set (n=58) and the efficacy analysis set (n=42). The full analysis set includes only patients who were infused with tisagenlecleucel-T; the efficacy analysis set includes only patients for whom there is at least 6 months between infusion and the data cut off (6th October 2017), which was used for the ORR outcome. Similarly, to ELIANA, the ERG requested data on the full ITT population all patients enrolled in the trial, which the company provided in the points of clarification response (Appendix, Table 31 Patient baseline characteristics for the full ITT population in ELIANA, ENSIGN and B2101J. Clinical advice to the ERG was that the ENSIGN population is broadly generalisable to the NHS r/r B-cell ALL patients.

4.2.1.3 Key properties of B2101J

B2101J is an ongoing, phase I/IIa, single centre, single-arm, open-label study that is evaluating tisagenlecleucel-T in ▮ patients with r/r B-cell ALL. The full ITT population, which includes all enrolled patients, comprised of ▮ patients. Basic details of the different analysis datasets are presented in Table 8 of the CS (p42), which includes the cohorts: the enrolled set (n=▮) and the full analysis set (n=▮). The baseline characteristics were reported for the full analysis set (▮ patients) rather than the full ITT population (▮ patients) in Table 6 of the CS (p40). The company provided these for the full ITT population in the points of clarification response. Clinical advice to the ERG was that B2101J population is broadly generalisable to the NHS r/r B-cell ALL patients. However, B2101J had a broader inclusion criteria, allowing inclusion of all patients with B-cell ALL rather than only primary refractory patients and patients in second or further relapse. Therefore, the number of patients with none or one previous relapse was ▮▮%. This is higher than would be expected in the eligible NHS population as tisagenlecleucel-T is mainly intended for patients with second or greater relapse. Furthermore, B2101J had a multiple infusion dosing regimen for tisagenlecleucel-T rather than a single infusion, which is the intended method of administration in the license.

4.2.2 Results of the Tisagenlecleucel-T trials

4.2.2.1 ELIANA

The primary outcome was ORR (defined as the proportion of patients with a best overall response of CR or CRi during the 3 months after tisagenlecleucel-T administration). For the efficacy analysis set (only patients infused with tisagenlecleucel-T), the ORR was ███%, including █% with CR, at the data cut-off (median follow up ███ months). Of these patients ███% were bone marrow negative. The median duration of response had not been reached at the data cut-off as ███% of patients who had achieved a best overall response of CR or CRi had not relapsed. The ERG notes that the efficacy analysis set was used for these outcomes, which does not include patients who were enrolled but not infused with tisagenlecleucel-T.

The CS reported the Kaplan-Meier curves for event-free survival (EFS) and OS for the full-analysis set, which excluded patients who were enrolled but not infused with tisagenlecleucel-T. The ERG requested Kaplan-Meier curves for the full ITT population, starting at the date of enrolment rather than the date of infusion, which are presented below in Figure 2 and Figure 3. The ERG notes that it is important to assess the full ITT population results since the delay between the decision to treat and receipt of treatment, is likely to be longer for tisagenlecleucel-T when compared to current treatment. Consequently, some of the ██ patients who were assigned tisagenlecleucel-T but were unable to receive it may have missed out on the opportunity of receiving another line of salvage chemotherapy.

Including the full ITT population reduces the overall EFS and OS rates (when compared to Table 2. Approximately ██ are event-free at 12 months, and ██ are alive at 12 months. The CS suggests the data support the potential for durable remissions and a high probability of long-term survival as the curves have long tails after 12 months for the EFS and OS plots. However, the ERG notes that from month 12 onwards the Kaplan-Meier plot for OS is heavily influenced by censoring of data. Due to the large proportion of patients censored there is substantial uncertainty regarding the longer-term EFS and OS rates. Longer follow up is required to reduce this uncertainty; the ERG's clinical advisor suggested a 5-year follow up would be a better indicator for considering the curative intent of tisagenlecleucel-T.

Figure 2 Kaplan-Meier curve for EFS from enrolment in ELIANA
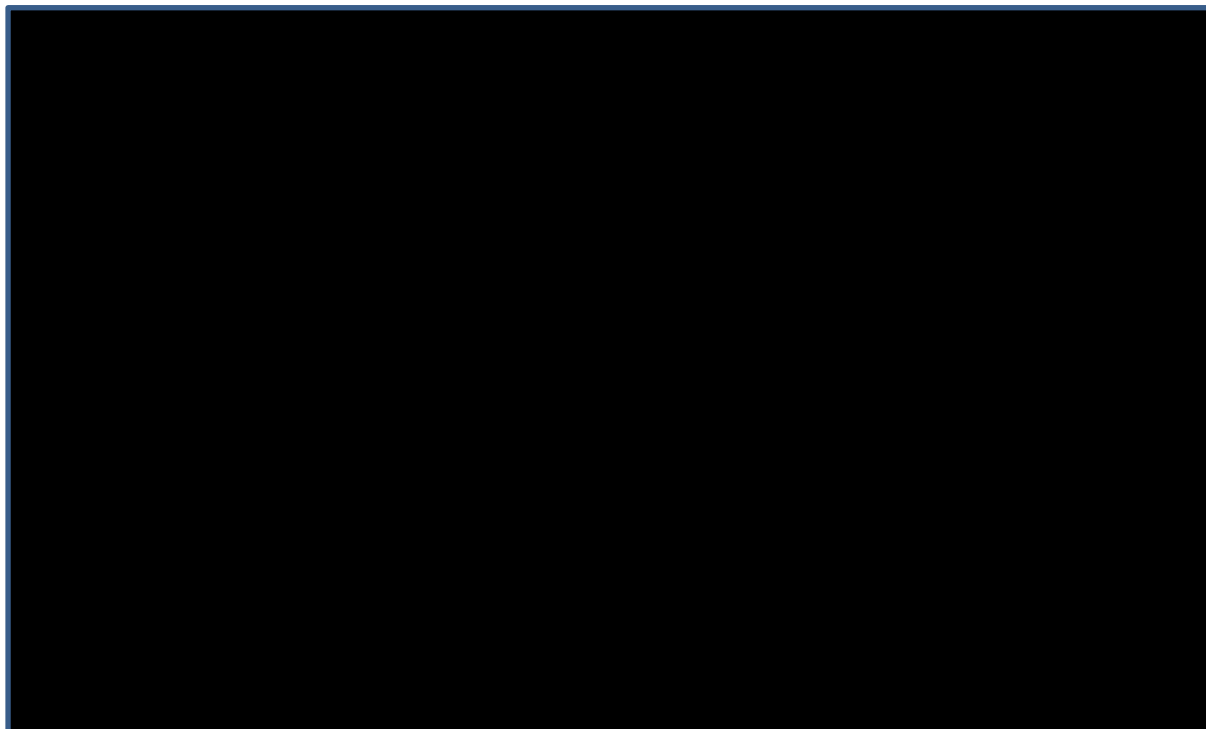
Figure 3 Kaplan-Meier curve for OS from enrolment in ELIANA
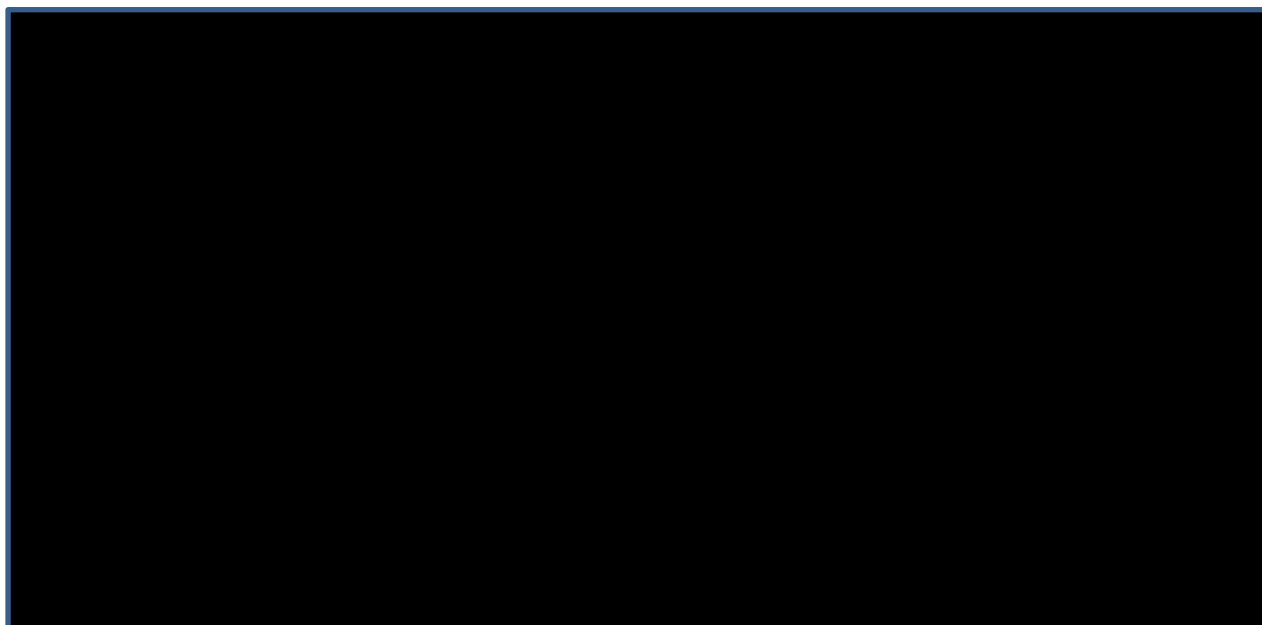
The ERG also requested KM curves of EFS and OS rates split by whether the patient received allo-SCT after infusion with tisagenlecleucel-T. The KM curve for OS (Figure 4) showed patients who received an allo-SCT after infusion had a higher rate of overall survival at 6, 12 and 20 months compared to patients who did not have an allo-SCT post infusion. EFS (Figure 5) did not differ significantly between the two groups. The proportion of patients who received an allo-SCT after

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infusion in ELIANA is concerning considering the curative intent of tisagenlecleucel-T. The ERG requested clarification from the company regarding the use of allo-SCT to consolidate tisagenlecleucel-T induced remission. The company responded stating that the rate of patients receiving a subsequent allo-SCT in ELIANA (███%) is an overestimate of likely UK clinical practice. Some physicians in the US chose to consolidate remission with an allo-SCT but this would only be an option in the UK if a patient suffers a relapse after tisagenlecleucel-T infusion.

Figure 4 Kaplan-Meier curve for OS by whether received post-infusion allo-SCT in ELIANA
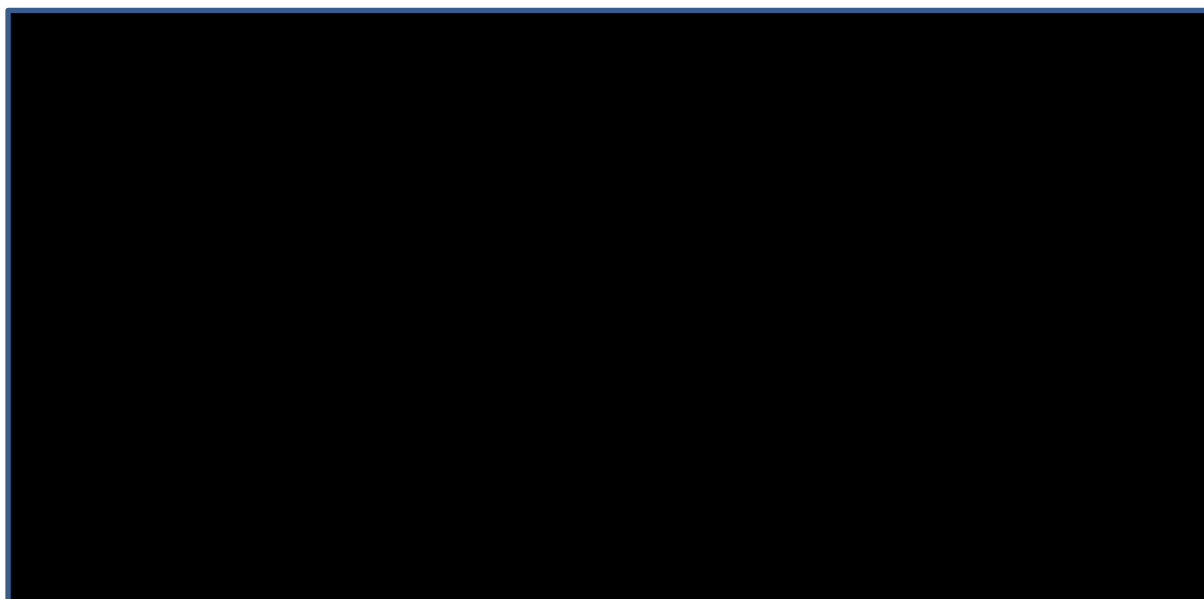
Figure 5 Kaplan-Meier curve for EFS (without censoring for allo-SCT) by whether received post-infusion allo-SCT in ELIANA
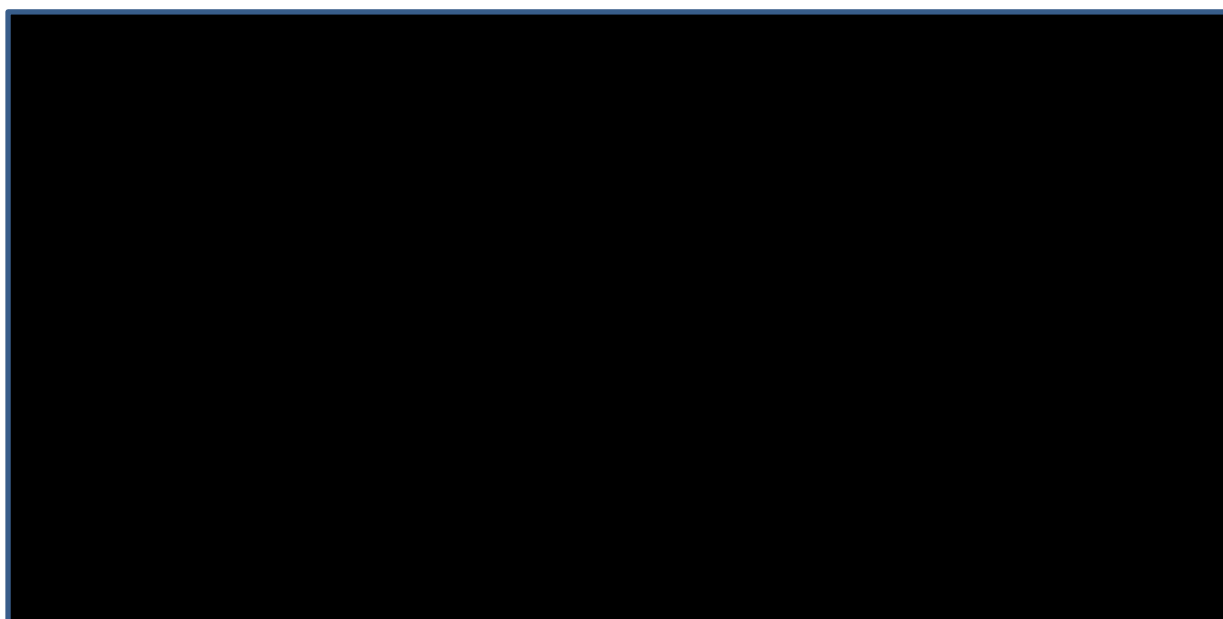
The CS included pre-specified ORR subgroup analyses for subgroups with at least five patients (presented in section B.2.7). However, these were not available for the latest data cut off (31st Dec 2017) but only for the data cut-off 25th April 2017. The CS concluded that the ORR was consistently ≥ 55% across all subgroups confirming the robustness of the primary analysis. However, these analyses were only done in the full analysis set not the full ITT population.

Patient reported outcomes

Patient reported outcomes were assessed using the paediatric quality of life questionnaire (PedsQL) and the EQ-5d-3L in patients who had achieved CR/CRi. Only patients ≥ 8 years only were included, with 44 patients assessed by PedsQL and 41 patients assessed by EQ-5d-3L. There were clinically meaningful differences observed between baseline and time points at 6, 12 and 18 months for both the PedsQL and EQ-5d-3L (Figure 6). However, there were a small proportion of patients past month 12 and only patients older than 8 years old were assessed. Therefore, these results may not be fully representative of the trial population.

Figure 6 Summary of PedsQL and EQVAS scores in ELIANA
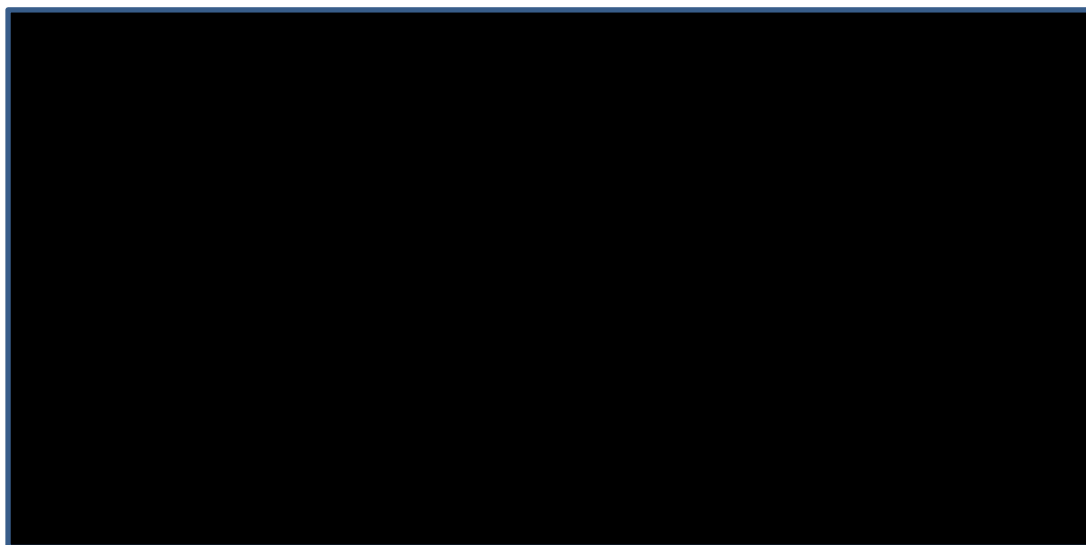
4.2.2.2 ENSIGN

For the efficacy analysis set (only patients infused with tisagenlecleucel-T) of 42 patients, the ORR was 69.0%, including 64.3% with CR, at the latest data cut-off (median follow up 19.6 months). Of the patients who achieved an overall remission rate of CR or CRi, 64.3% of patients were bone marrow negative. The median duration of response had not been reached at the data cut-off as 69.0% of patients who had achieved a best overall response of CR or CRi had not relapsed.

As with ELIANA, the ERG requested Kaplan-Meier curves for EFS and OS for ENSIGN starting at the date of enrolment rather than the date of infusion, which are presented below in Figure 7 and Figure 8, respectively. There were 15 patients enrolled in the trial who did not receive tisagenlecleucel-T. Including the full ITT population reduces the overall EFS and OS rates, when compared to the results in Table 2 Summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J (adapted from Table 11 of the CS on page 47). Approximately ▇▇ are event-free at 12 months, and ▇ are alive at 12 months.

The median OS should be interpreted with caution, as there are small numbers of patients at risk beyond 16 months. Furthermore, the KM plots for EFS and OS are heavily censored. Therefore, there is substantial uncertainty regarding the true effect of tisagenlecleucel-T on EFS and OS in the ENSIGN trial. A median follow-up of 19.6 months is inadequate in illustrating the effect of tisagenlecleucel-T beyond 24 months, which is what is required when considering tisagenlecleucel-T as a curative treatment.

Figure 7 Kaplan-Meier curve for EFS from enrolment for ENSIGN
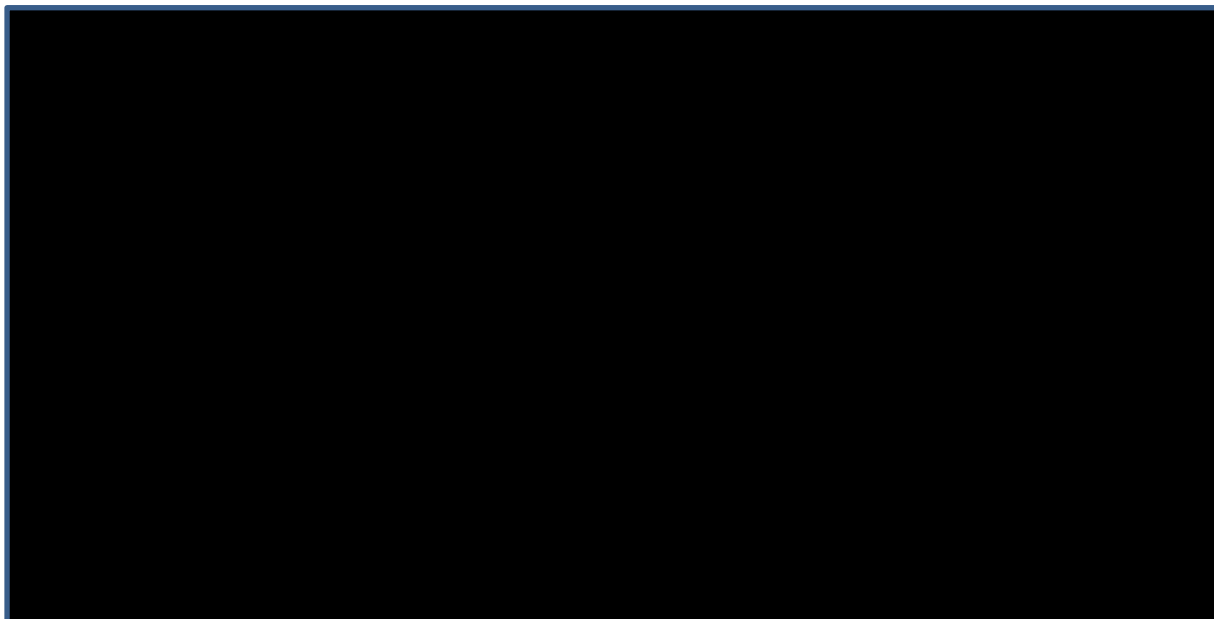
Figure 8 Kaplan-Meier curve for OS from enrolment for ENSIGN
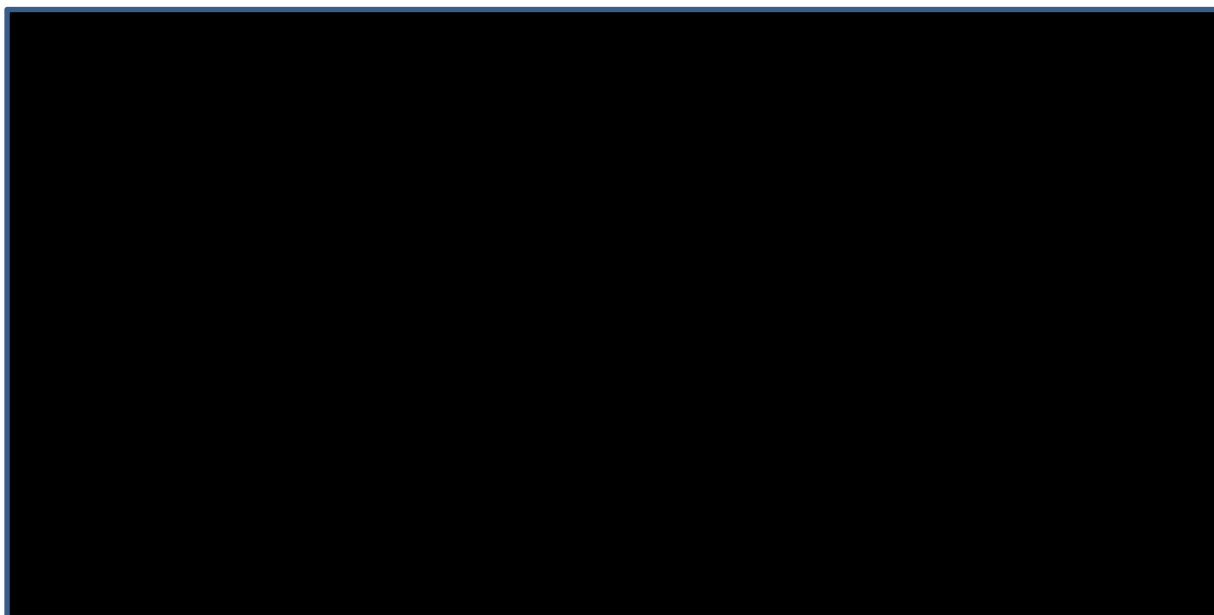
As with ELIANA, the ERG also requested KM curves of EFS and OS rates split by whether the patient received allo-SCT after infusion with tisagenlecleucel-T for ENSIGN. The KM curve for OS (Figure 9) showed patients who received an allo-SCT after infusion had a higher rate of overall survival at 6, 12 and 20 months compared to patients who did not have an allo-SCT post infusion. However, the EFS curve (Figure 10) showed that patients who had a previous allo-SCT had a higher rate of EFS until month 6, after which both groups had similar rates of EFS. The proportion of patients who received an allo-SCT after infusion in ENSIGN was less than in ELIANA (%) but

is still concerning. The company stated that it is an overestimate of likely UK clinical practice, however the proportion of patients receiving post-infusion allo-SCT in B2101J was also high (█████%). Therefore, there is considerable uncertainty regarding the role of tisagenlecleucel-T as a curative treatment.

Figure 9 Kaplan-Meier curve for OS whether received post-infusion allo-SCT in ENSIGN
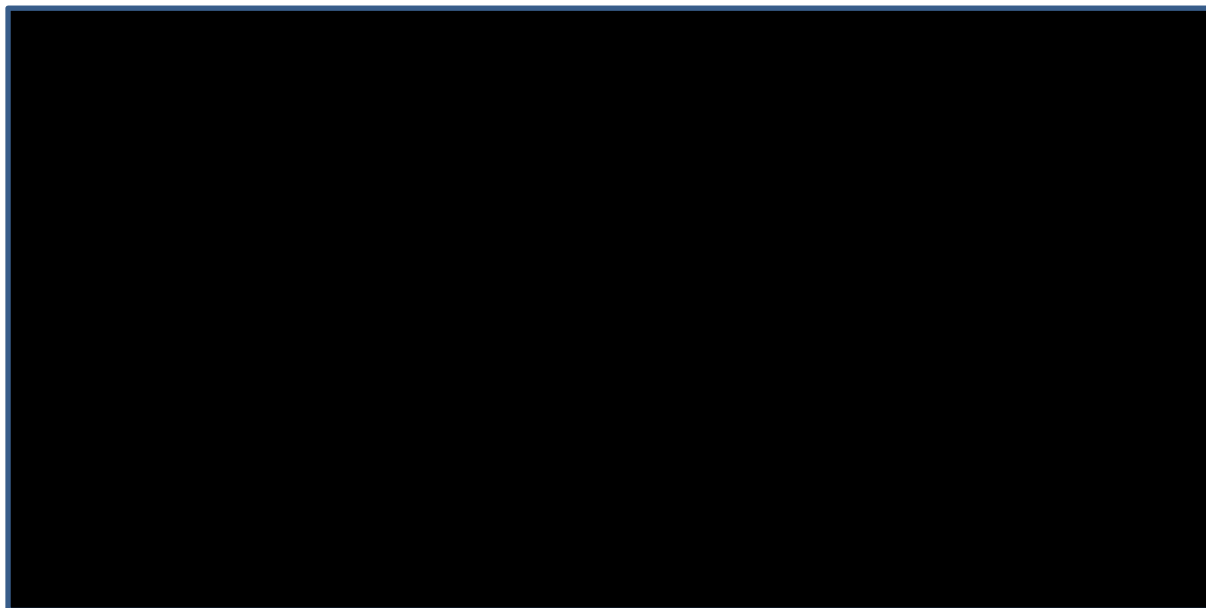
Figure 10 Kaplan-Meier curve for EFS (without censoring for allo-SCT) whether received post-infusion allo-SCT in ENSIGN
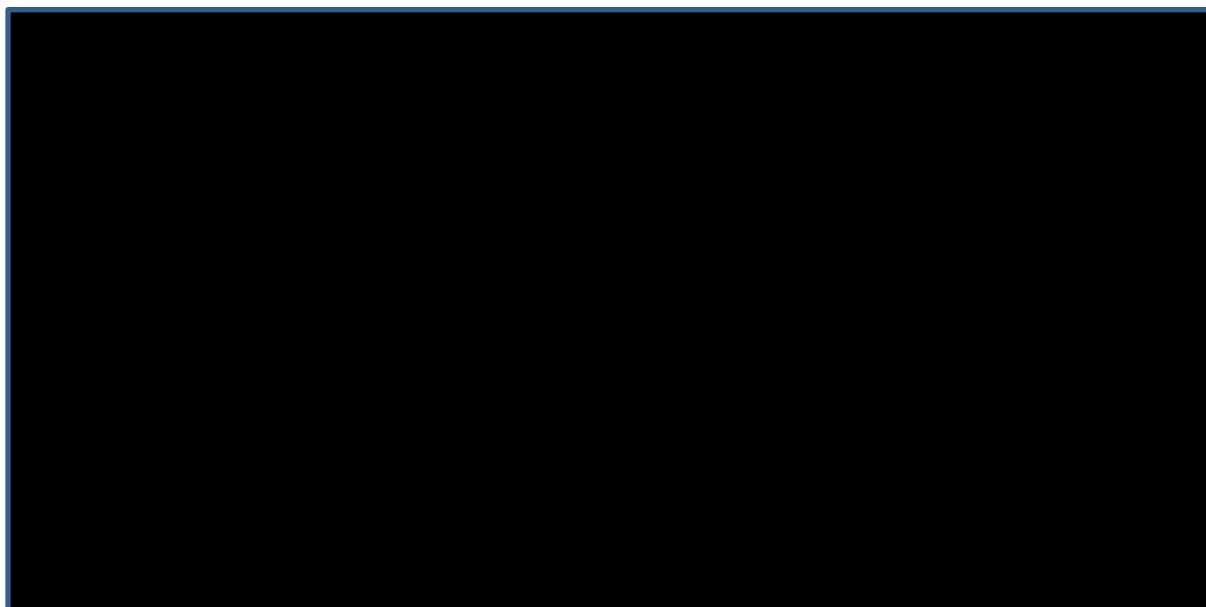
4.2.2.3   B2010J

For the full analysis set (only patients infused with tisagenlecleucel-T) of ▓ patients, the ORR was ▓▓▓%, including ▓▓▓% achieving CR, at the latest data cut-off (median follow up ▓▓▓ months). Of the patients who achieved an overall remission rate of CR or CRi, ▓▓▓% of patients were bone marrow negative. The median duration of response at the data cut-off was ▓▓▓ months and ▓▓▓% of patients who had achieved a best overall response of CR or CRi had not suffered an event. The ERG notes that these outcomes were only assessed in the patients who were infused with tisagenlecleucel-T, rather than all patients enrolled in the study.

As with ELIANA and ENSIGN, the ERG requested Kaplan-Meier curves for EFS and OS for B2101J starting at the date of enrolment rather than the date of infusion. These are presented below in Figure 11and Figure 12 respectively. The ERG also requested Kaplan-Meier plots of OS with censoring for allo-SCT, which are presented in Figure 13 and shows a median overall survival of ▓▓▓ months. The EFS and OS results are summarised in Table 2 Summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J (adapted from Table 11 of the CS on page 47) Although, the results show a beneficial effect of tisagenlecleucel-T on EFS and OS, the median OS should be interpreted with caution, as there are small numbers of patients at risk beyond 36 months. Additionally, the ERG notes that there is uncertainty regarding the impact of the multiple infusion method of tisagenlecleucel-T in B2101, which may have contributed to improved drug persistence and therefore biased long-term outcomes.

Figure 11 Kaplan-Meier curve for EFS from enrolment in B2101J
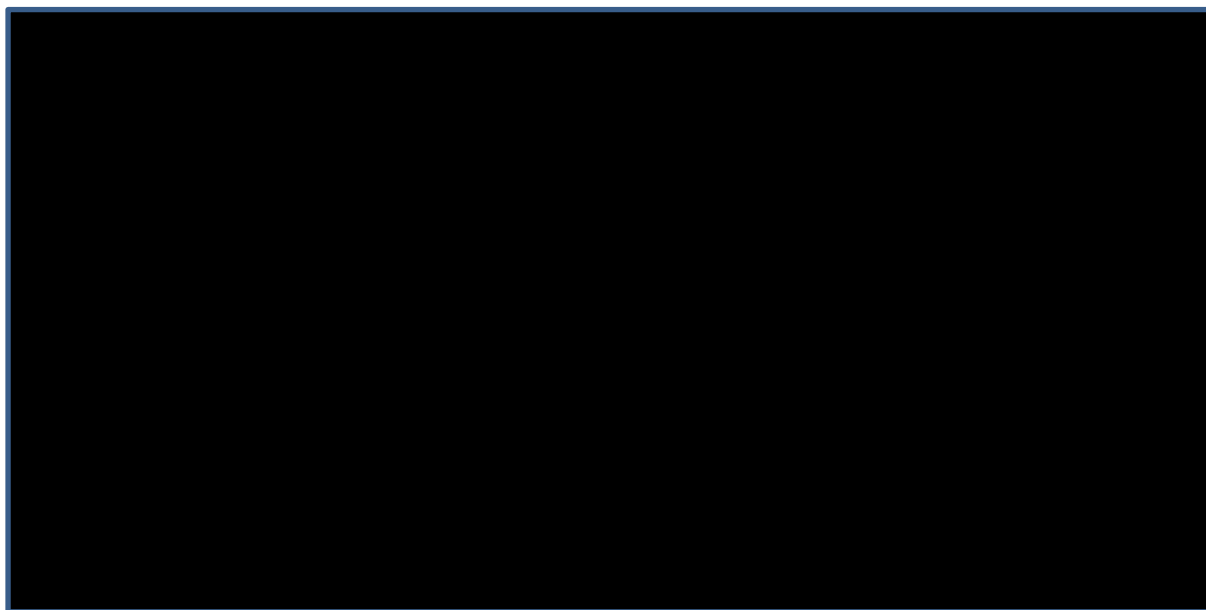
Figure 12 Kaplan-Meier curve for OS from enrolment in B2101J
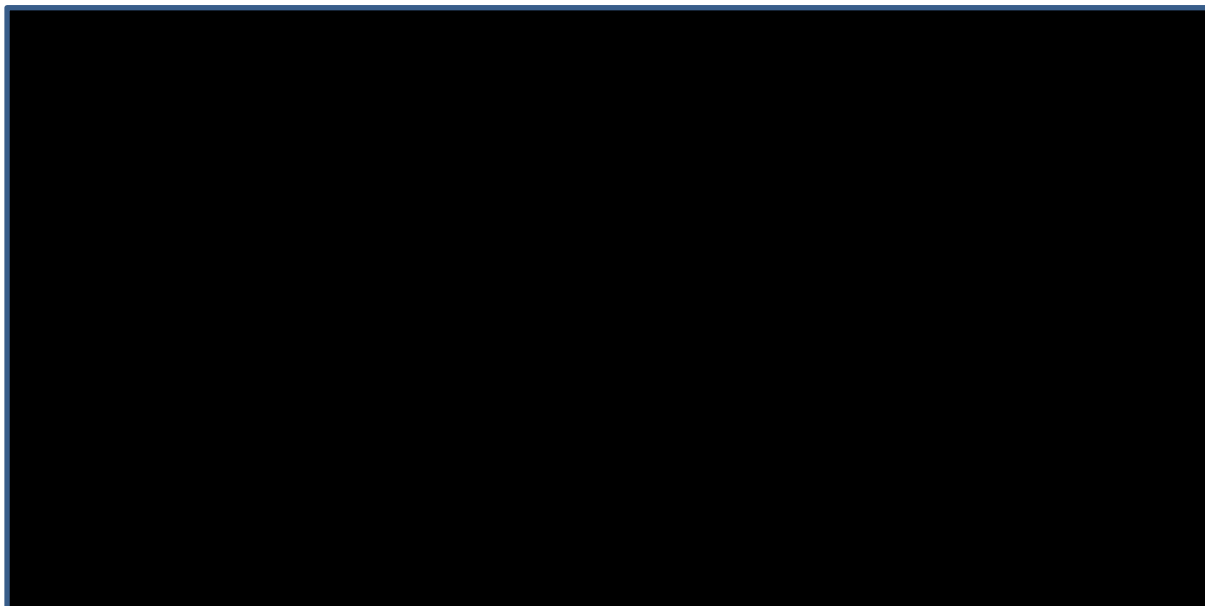
Figure 13 Kaplan-Meier curve of OS from B2101J with censoring for allo-SCT
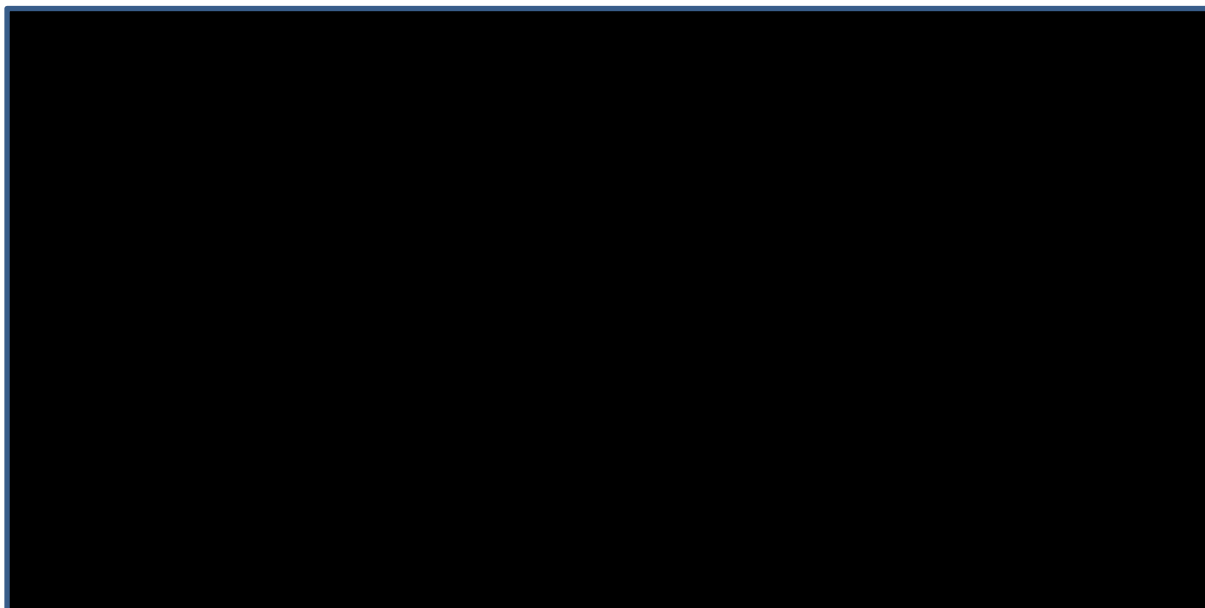
4.2.3   Meta-analysis

The CS pooled data from the three tisagenlecleucel-T studies (ENSIGN, ELIANA and B2101J) as part of a meta-analysis. This was done to increase the overall available sample size and to allow the use of the longest-term follow up data available. The CS assessed the comparability of the three trials focusing on study design, outcome definitions and patient baseline characteristics. Although, the definitions of EFS and OS, the main outcome measures informing the economic analysis, were

identical across all three studies there were a few differences in study design and baseline characteristics.

The pooled data included ▮▮ patients, for which EFS and OS were assessed (**Figure 14** and Figure 15, respectively). The CS reported the probability of being event-free was ▮▮% at one year, ▮▮% at two years and ▮▮% at 3 years. Median EFS was ▮▮ months and ▮▮% of patients reported an EFS event. Median OS was ▮▮ months and ▮▮% of patients had died following tisagenlecleucel-T infusion. The probability of survival at one year was ▮▮% and ▮▮% at 2 years However, the median OS should be interpreted with caution, as there are very small numbers of patients at risk beyond 38 months.

It is of particular importance to note that these analyses are not for the full ITT population, only for patients who have been infused with tisagenlecleucel-T. As discussed for the individual trials, this is likely to overstate the benefit of tisagenlecleucel-T because it excluded the children who did not receive an infusion, who are probably of poorer prognosis.

Figure 14 Kaplan-Meier curve for EFS in ELIANA, ENSIGN, B2110J and the pooled analysis a
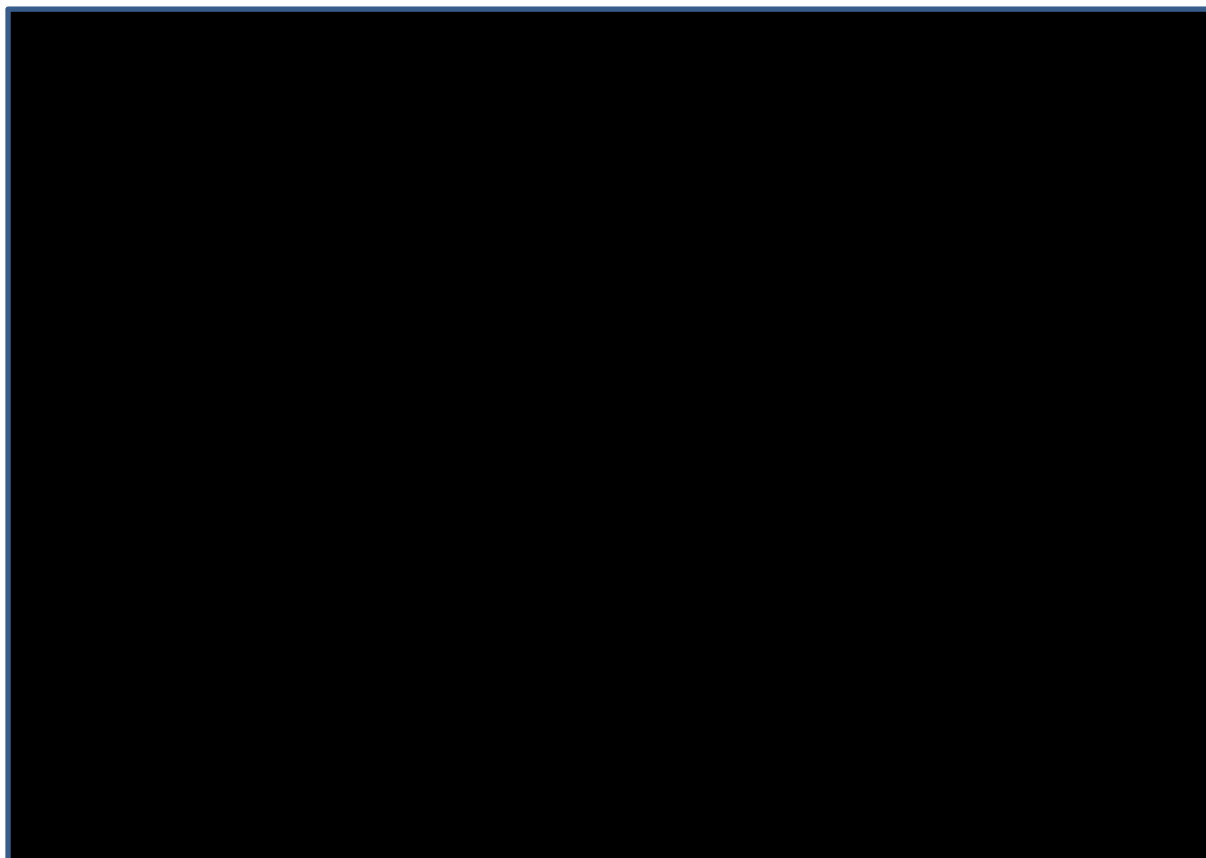
Figure 15 Kaplan-Meier curve of OS in ELIANA, ENSIGN, B2101J and the pooled analysis
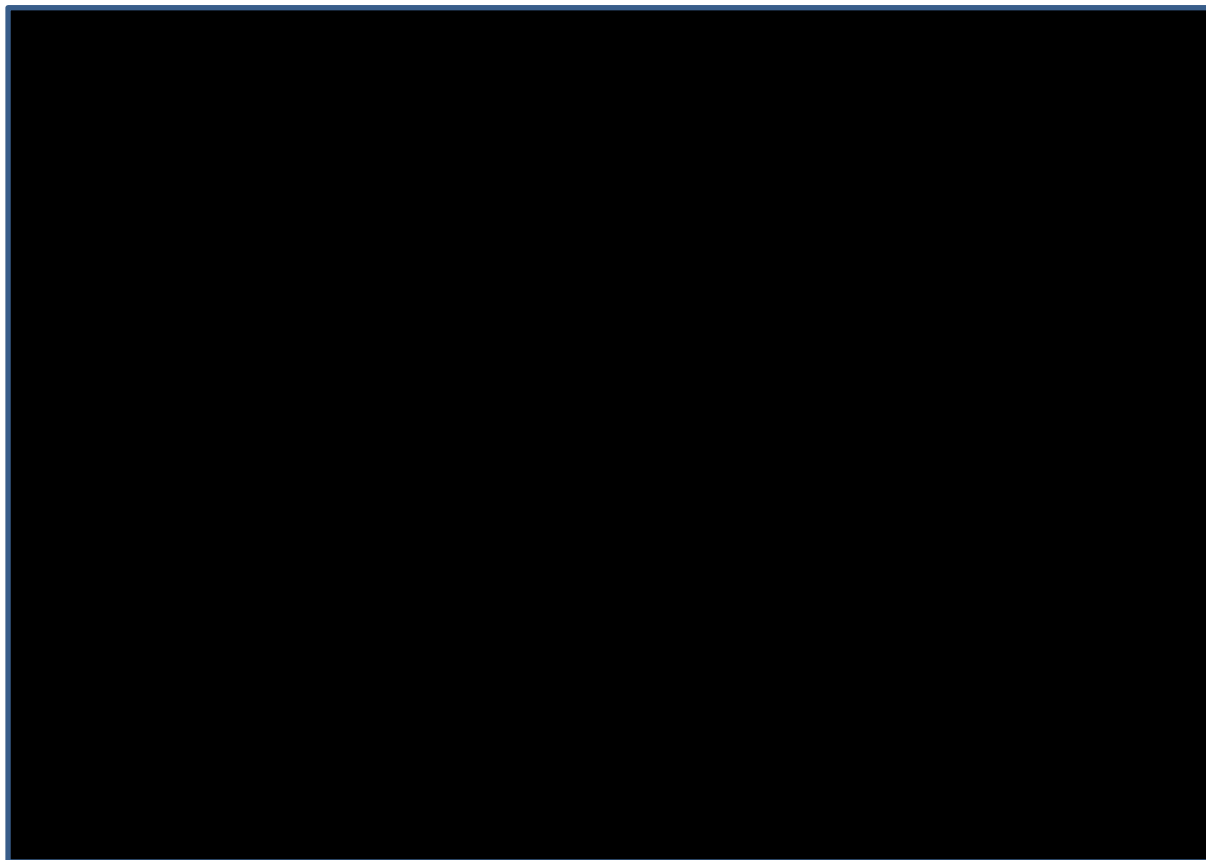
4.2.4   Adverse events of tisagenlecleucel-T

Data on adverse events were derived from a total of ███ patients from the ELIANA, ENSIGN and B2101J trials. All patients had received at least one infusion of tisagenlecleucel-T. The adverse events were reported in the CS on pages 72-84.

All patients had an adverse event (AE) and in all three trials most had an AE that was suspected to be study drug-related (████%, ████% and ███% in ELIANA, ENSIGN and B2101J, respectively). Serious adverse events (SAE) were reported in ████%, 77.6% and ████% of patients in the ELIANA, ENSIGN and B2101J trials, respectively (Table 21 of the CS). ████ patients in ELIANA and ████ patients in ENSIGN died due to an AE. There were ██ deaths in B2101J, but the CS did not report how many were due to AE.

The CS reported that cytokine release syndrome (CRS), pyrexia, decreased appetite and hypogammaglobulinemia are the most frequent AE and SAE overall. The most common SAE was CRS, which occurred at any grade in ████%, ████% and ████% of patients in ELIANA, ENSIGN and B2101J, respectively. The most common SAE at grade 3 was febrile neutropenia in both ENSIGN (████%) and B2101J (████%) but was CRS (████%) in ELIANA.

The CS presented a table (p76 of CS) of adverse events occurring in at least 10% of patients post tisagenlecleucel-T infusion. CRS was the most common in ELIANA (████%) and ENSIGN (████%), whereas white blood cell count decreased was the most common in B2101J (████%). The ERG requested data on B-cell aplasia (an absence of B-cells) in all three trials, as this was not reported in the CS. The company provided KM curves for time to B-cell recovery in patients who achieved CR or CRi in ELIANA and ENSIGN, which are presented in the Appendice. These data were not available for B2101J. In both ELIANA and ENSIGN, the probability of B-cell recovery was approximately ██% at month 12, this remained the same at month 24. This suggests that long-term follow up is needed to assess the late-effects of B-cell aplasia, which in turn has ongoing resource impact as it requires treatment with IVIG. This is discussed in more detail in section 5.

4.3   Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1   Comparator treatment studies

The CS used the two studies von Stackelberg *et al*. (28) and Jeha *et al*. (21) as evidence on the comparator treatments blinatumomab and salvage chemotherapy (FLA-IDA), respectively. The selection process of these studies is described earlier in section 4.1.2. There are concerns regarding the comparability of these trials to the tisagenlecleucel-T trials, which are discussed below.

4.3.1.1   Blinatumomab

The study used as evidence for blinatumomab as a comparator is von Stackelberg *et al*. (2016)[8]. It is a phase I/II single-arm, multi-centre, open-label study in paediatric r/r B-ALL patients. The study population consists of 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. However, in practice, both the clinical advisor and the CS state that blinatumomab would not typically be given to patients in second or later relapse due to it being used earlier in the treatment pathway. This raises concern regarding the validity of blinatumomab as a comparator to tisagenlecleucel-T.

The ERG notes various differences between the von Stackelberg *et al*. and tisagenlecleucel-T studies. The tisagenlecleucel-T studies recruited patients up to the age of 25 years, whereas von Stackelberg *et al*. only recruited patients under 18 years old. The ELIANA and ENSIGN studies required patients to have ≥ 5% bone marrow blasts, whereas von Stackelberg *et al*. specified > 25% bone marrow blasts. Patients in von Stackelberg *et al.* may therefore have had more progressive disease at baseline. A substantial proportion (22%) of patients in the von Stackelberg trial went on to experience CD19-negative relapse. Therefore, these patients would not be eligible to receive tisagenlecleucel-T.

Von Stackelberg *et al.* reported that the cohort had particularly unfavourable characteristics as 71% of patients had relapsed within 6 months of the previous treatment attempt, which has been shown to be a determinant of poor prognosis in B-cell ALL patients. The population considered was very high risk based on tumour load, multiple prior relapses and short interval between latest treatment and start of blinatumomab. This may have led to a worse outcome than would otherwise be expected for patients being treated with blinatumomab.

The ERG does not consider this study to represent suitable evidence of an appropriate comparator.

4.3.1.2 Clofarabine and salvage chemotherapy (FLA-IDA)

The CS did not identify any studies evaluating salvage chemotherapy (FLA-IDA). The CS chose to use clofarabine as a proxy for salvage chemotherapy. The ERG notes that no clinical evidence was provided to support the equivalence of FLA-IDA and clofarabine, so the ERG questions the validity of this choice of proxy.

Six studies evaluating clofarabine were identified. Studies that had an OS of around 9 months were excluded and studies that evaluated clofarabine combination therapy rather than monotherapy were excluded. The ERG considers that excluding trials on this basis was not justifiable.

The CS considered Jeha *et al.* (2006) [7] to be the most appropriate source of clinical data for the salvage chemotherapy comparator. Jeha *et al.* is a phase II single-arm, multicentre, study in r/r paediatric ALL patients treated with clofarabine therapy. The study consists of 61 patients who received clofarabine intravenously over two hours daily for five days.

The ERG noted several differences in study design and baseline characteristics between Jeha *et al.* and the tisagenlecleucel-T studies. For example, there were 30% of patients in Jeha *et al.* who had a prior allo-SCT, this is much lower than the proportion who received prior allo-SCT in the tisagenlecleucel-T trials (██%). The age of the trial (2006) is also concerning as the ERG considers that care may have improved over time. Overall, the ERG considers that Jeha *et al.* has areas of uncertainty and substantial differences with the tisagenlecleucel-T studies, therefore comparing these studies would produce unreliable results.

The overall remission rate was 20%, with a median overall survival of 13 weeks. The ERG requested OS and EFS Kaplan-Meier curves for Jeha *et al.*, however only OS curves were available, which are presented in Figure 16.

Figure 16 Kaplan-Meier curve for overall survival from Jeha *et al*. (2006)
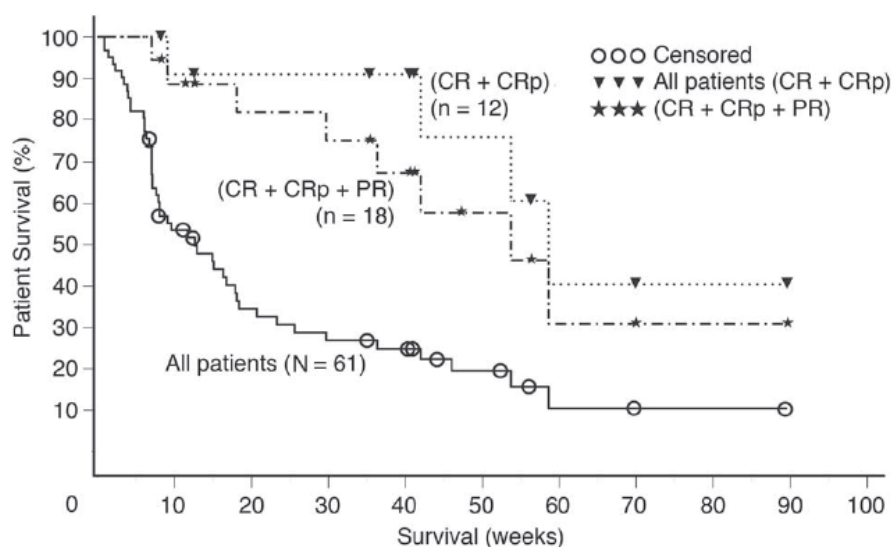
The ERG notes that the six trials identified by the company as evidence for clofarabine monotherapy or combination therapy also differ considerably in baseline characteristics and study design with the tisagenlecleucel-T studies. The patients recruited to the tisagenlecleucel-T studies seem to be inherently different to the patients recruited to the six clofarabine trials. The pre-infusion OS data from enrolment to infusion of the three tisagenlecleucel-T trials shows that there are significantly fewer deaths before infusion with tisagenlecleucel-T than in any of the six clofarabine studies. Although, the ERG recognises that this difference may be partly due to the toxicity of clofarabine, comparing these trials does not seem appropriate. The ERG requested EFS and OS K-M curves for all six trials, but only overall survival K-M curves were available, which are presented in the Appendix, Figure 34 Kaplan-Meier curve for OS from Cooper *et al*. (2013) to Figure 37 Kaplan-Meier curve for OS from Miano *et al*. (2012)

The ERG identified two further studies as evidence for FLA-IDA, which were not reported in the CS.

Sun *et al*. (2017) [4], was a retrospective analysis of 325 patients with r/r B-ALL. The study included patients ≤ 21 years old who underwent chemotherapy-based salvage treatment for primary induction failure, or with ≥2 occasions of relapsed disease; or failure to achieve remission after first or more salvage treatment attempts. The baseline characteristics of the patients in Sun *et al*. seem to be similar to the patient characteristics in the tisagenlecleucel-T studies. The overall CR rate was 51±3.9% after the second salvage attempt and <40% after the third and subsequent attempts. This suggests that

patients with r/r B-ALL have substantially better prognosis than shown in the comparator studies identified by the company.

Kuhlen *et al*. (2017), was a retrospective analysis of 242 paediatric patients with r/r B-cell ALL in first relapse post allo-SCT, treated with multi-drug chemotherapy. The 3-year probability of EFS and OS was 15% and 20%, respectively. The baseline characteristics of the patients in this trial are similar to the patient characteristics in the tisagenlecleucel-T trials. The much larger sample size and longer follow-up provides a more reliable and robust data-set compared to the studies identified by the company. The study only includes patients who have had an allo-SCT, whereas only ███% of patients in the tisagenlecleucel-T trials had a prior allo-SCT. This may under-estimate OS in Kuhlen *et al*.

The ERG considers these two studies to be more appropriate and reliable than the trials identified by the company.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Description and critique of the company's approach to creating and analysing a comparative clinical effectiveness dataset

The company's approach to comparing the effectiveness of tisagenlecleucel-T to standard of care treatments was to conduct a matched-adjusted treatment comparison (MAIC) with patient-level data from the pooled tisagenlecleucel-T population and summary-level data from the von Stackelberg *et al*. and Jeha *et al*. populations.

Adjusting for all baseline imbalances was not possible and so the characteristics which had the most effect on the MAIC results were prioritised. The MAIC with blinatumomab and salvage chemotherapy was able to adjust for a few baseline characteristics including the number of previous relapses, median number of months since last relapse and proportion of patients with prior allo-SCT. However, several baseline imbalances could not be adjusted including median age, geographic region, genetic abnormalities and the proportion of primary refractory patients. This was mainly due to avoiding a substantial loss in sample size and poor reporting by the studies. The unadjusted characteristics are key prognostic variables, therefore being unable to minimise these differences increases the risk of producing unreliable and inaccurate results [37].

The CS presented the naïve comparison and the MAIC comparison for both blinatumomab and salvage chemotherapy, which are presented in Table 3. The hazard ratios show a positive effect of tisagenlecleucel-T compared to both blinatumomab and salvage chemotherapy. The Kaplan-Meier curves in Figure 17 and Figure 18 show tisagenlecleucel-T has a superior OS and that both the naïve

comparison and the MAIC comparison are similar. This suggests that patient differences do not fully explain the difference in outcomes. However, a main limitation was not adjusting all key baseline characteristics and structural differences between trials outlined above. A MAIC also does not consider unobserved cross-trial differences, which may result in residual confounding[38]. Therefore, these limitations suggest that the populations being compared may still be substantially different and there is considerable uncertainty regarding the impact of these differences on the OS estimates.

Table 3 Overall survival hazard ratios (adapted from Table 20, page 70 of the CS)

Adjustment scenario	Naïve comparison		MAIC comparison	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Tisagenlecleucel-T vs blinatumomab	██████████	████	██████████	███
Tisagenlecleucel-T vs salvage chemotherapy	██████████	█████	██████████	████

Figure 17 Overall survival for tisagenlecleucel-T versus blinatumomab
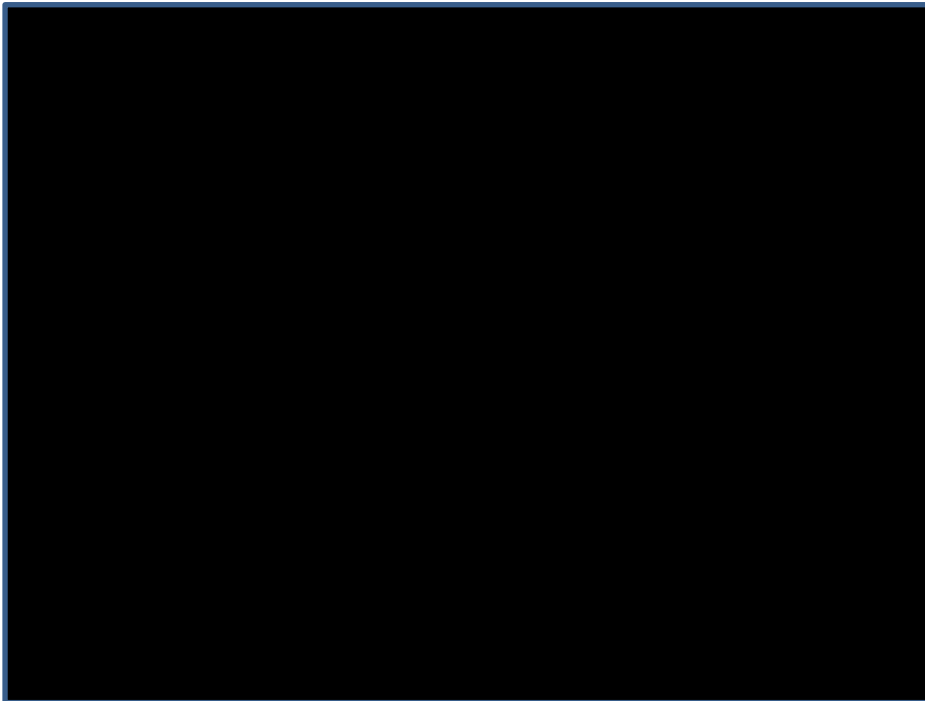
Figure 18 Overall survival for tisagenlecleucel-T versus salvage chemotherapy
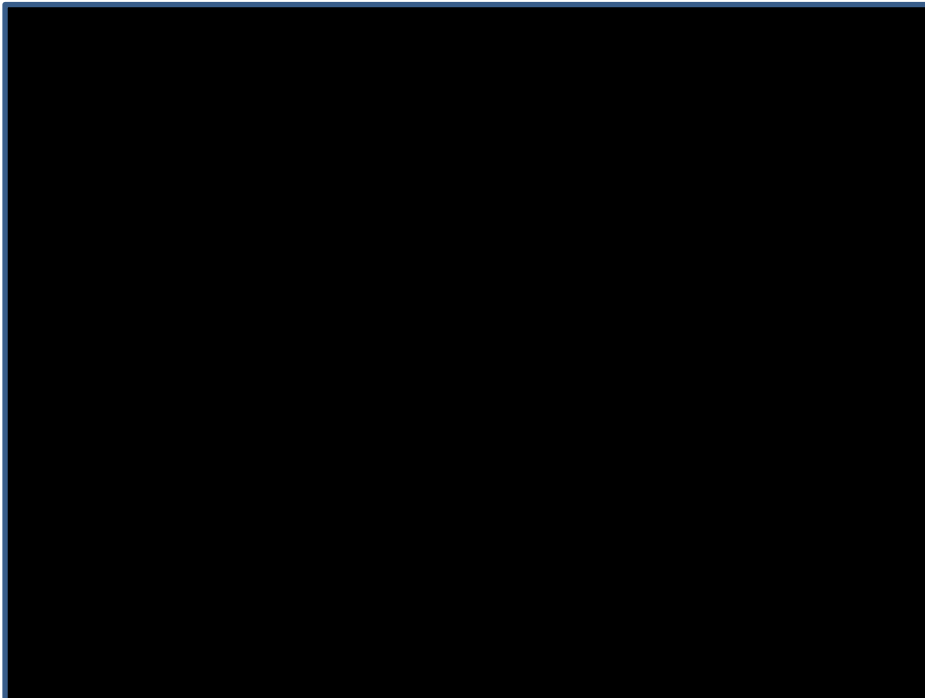
4.5   Additional work on clinical effectiveness undertaken by the ERG

No additional work was carried out by the ERG.

4.6   Conclusions of the clinical effectiveness section

The CS included data from three ongoing, single-arm, phase II, open-label studies: ELIANA, ENSIGN and B2101J. All three trials evaluated tisagenlecleucel-T in paediatric and young adult patients with r/r B-cell ALL. The full ITT populations for ELIANA, ENSIGN and B2101J were █ patients, 73 patients and █ patients.

The ERG noted some limitations about 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. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. The ERG recognises a delay between enrolment and infusion with tisagenlecleucel-T. The median time between enrolment and infusion of tisagenlecleucel-T in ELIANA, ENSIGN and B2101J was █ days, 41 days and █ days. This is substantially longer than the 3 to 4 weeks estimated in the CS, which has considerable implication for eligible patients due to the pace of disease progression and their short-estimated life expectancy.

The CS reported results for the full-analysis set, which excluded patients who were enrolled but not infused with tisagenlecleucel-T. Some of the patients who were assigned tisagenlecleucel-T but were unable to receive it may have missed out on the opportunity of receiving another line of salvage chemotherapy. The results show that patients enrolled but not infused with tisagenlecleucel-T have a very poor prognosis.

The K-M curves for all patients enrolled in the trials, show a beneficial effect of tisagenlecleucel-T on EFS and OS. However, the ERG notes that the ELIANA KM plots for OS are heavily influenced by censoring of data. In ENSIGN and B2101J the median OS should be interpreted with caution, as there are small numbers of patients at risk beyond 18 and 36 months, respectively. Longer follow up is required to reduce this uncertainty; the ERG's clinical advisor suggested a 5-year follow up would be a better indicator for considering the curative intent of tisagenlecleucel-T.

The CS pooled data from the three tisagenlecleucel-T studies as part of a meta-analysis. These analyses are not for the full ITT population, only for patients who have been infused with tisagenlecleucel-T. This is likely to overstate the benefit of tisagenlecleucel-T because it excluded the children who did not receive an infusion, who are probably of poorer prognosis. The CS reported the probability of EFS and OS at two-years was ███ % and ███ %. However, the median OS should be interpreted with caution, as there are very small numbers of patients at risk beyond 38 months.

The CS used the two studies von Stackelberg *et al*. and Jeha *et al*. as evidence on the comparator treatments blinatumomab and salvage chemotherapy (FLA-IDA), respectively. There are concerns regarding the comparability of these trials to the tisagenlecleucel-T trials. The ERG does not consider Stackelberg *et al*. or Jeha et a. as suitable evidence of appropriate comparators.

The ERG identified a further study as evidence for FLA-IDA, which was not reported in the CS. Kuhlen *et al*. (2017), was a retrospective analysis of 242 paediatric patients with r/r B-cell ALL in first relapse post allo-SCT. The 3-year probability of EFS and OS was 15% and 20%, respectively. The much larger sample size and longer follow-up provides a more reliable and robust data-set compared to the studies identified by the company.

The company presented a matched-adjusted treatment comparison (MAIC) with data from the pooled tisagenlecleucel-T population and from the Stackelberg *et al*. and Jeha *et al*. populations. The hazard ratios show a positive effect of tisagenlecleucel-T compared to both blinatumomab and salvage chemotherapy. However, the MAIC was not able to adjust all key baseline characteristics and structural differences between trials. Therefore, the populations being compared may still be substantially different and there is considerable uncertainty regarding the impact of these differences on the OS estimates.

5   Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation and a narrative review to highlight key assumptions and uncertainties

5.1   ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify relevant published cost-effectiveness studies of the treatment of young people (age<25) with r/r ALL. The ERG's critique of this systematic review is presented below.

5.1.1   Searches

The following databases were searched on 24 November 2017:

MEDLINE; MEDLINE In- Proccess; EMBASE; EconLit; American college of Physicians Journal club; Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), Cochrane Methodology Register (CMR); Database of Abstracts of Reviews of Effects (DARE), and NHS Economic Evaluation Database (NHSEED). The search strategy used is reproduced in Table 18 of Appendix G of the CS.

In addition to the above formal searches, HTA websites and conference proceedings from the last three years (2015, 2016, 2017) were hand searched to identify potentially relevant posters and abstracts.

The ERG considers the searches undertaken by the company to be appropriate.

5.1.2   Inclusion/exclusion criteria used for study selection

The eligibility criteria applied in the systematic review are summarised in Table 19 (Appendix G) of the CS and follow the usual PICOS framework. In brief, the review included any economic analyses and systematic reviews of treatments for young people (age<25) with r/r ALL. Articles were independently assessed by two reviewers against each eligibility criteria, with discrepancies reconciled by a third independent reviewer

The ERG considers that the inclusion/exclusion criteria appear to be appropriate, although some relevant studies in indirectly relevant populations such as adults with r/r ALL may have been missed.

5.1.3   Studies included and excluded in the cost effectiveness review

A total of 369 potentially relevant articles were identified in the cost-effectiveness review after deduplication of records identified in the search. Of these 363 were subsequently excluded at the primary screening stage, with the remaining 6 studies assessed in full, see PRISMA flow diagram summarising the selection process (Appendix G; Figure 7, CS).

In total, three studies were extracted from the identified publications. The studies were summarised in Table 20, 21, 22 and 23 (Appendix G of the CS), and a quality check of the studies was reported in Table 24 (Appendix G of the CS). In addition to the above a further three economic evaluations were identified in additional hand searches conducted by the company, following the completion of the cost-effectiveness review. These studies were summarised in Table 25, 26 and 27 (Appendix G of the CS). Because these three studies were identified separately from the systematic review, they were not included within the company's review or quality assessment.

Of the six studies identified in total, four evaluated the cost-effectives of tisagenlecleucel-T.[39-42] In brief these studies addressed the following decision problems:

- Hettle *et al.* (2017) [40] evaluated tisagenlecleucel-T compared with chemotherapy from a NHS and personal social services perspective. This evaluation was a mock appraisal conducted by a team at the University of York to explore the application of existing NICE appraisal methodology to regenerative medicines using hypothetical data.
- Snider *et al* [42] was an extension of the York developed model to investigate the potential economic value of tisagenlecleucel-T and took a UK societal perspective.
- Hao *et al* [39] was a company-sponsored evaluation which compared tisagenlecleucel-T with two clofarabine regimens, blinatumomab and standard care. This evaluation undertook a value based pricing analysis from a US third-party payer perspective.
- The US ICER [41] model was developed by US Institute for Clinical and Economic Review (US ICER) and compared tisagenlecleucel-T with clofarabine and BSC from a US third-party payer perspective.

Each of the four evaluations assessing tisagenlecleucel-T/CAR-T cells adopted somewhat different model structures. The Hao *et al* model consisted of solely a partitioned survival model, while the Snider *et al*, York, and US ICER models used hybrid model structures. The York and Snider models used a two part model consisting of i) a short-term decision tree characterising the period from the

initiation of treatment (CAR-T or chemotherapy) to the initial response assessment (approximately 2 months); (ii) a partitioned survival analysis model characterising survival after that point. The US ICER model extended this to a three part model consisting of

i) a short-term decision tree characterising the period from the initiation of treatment (CAR-T or chemotherapy) to the initial response assessment (approximately one month);

ii) a partitioned survival analysis model characterising the time period between the initial response assessment and five-years

iii) a Markov model from five-years until death. In all four models patients who were alive and responding to treatment at five-years were assumed to be long-term survivors and effectively 'cured'. Mortality after five years was then based on the general population age- and gender-adjusted all-cause risks of mortality, with adjustments made for excess mortality (using a standardised mortality ratio).

One-way sensitivity analyses and scenario analyses were undertaken in the Hao *et al* and US ICER developed model to identify the key drivers of model outcomes. The key drivers identified were the outcome discount rate, extrapolation of KM data; the utility estimate for responders to treatment health state, and the standardised mortality ratio and the duration.

5.1.4 Conclusions of the cost effectiveness review

The CS reported on four previous cost-effectiveness analyses assessing tisagenlecleucel/CAR-T cells for the treatment of young people (age<25) with r/r ALL. Two of these Snider *et al*[42] and Hettle *et al*[40] (the York model), took a UK perspective; but were based primarily on hypothetical data. As such, they should not be used to make judgements about the cost-effectiveness of tisagenlecleucel-T. The company review also identified two recently published US studies evaluating cost-effectiveness of tisagenlecleucel-T in young people (age<25) with r/r ALL. The inevitable differences between the US health care system and the NHS, however, make it difficult to generalise the results of these models.

Given these limitations with the previous economic evaluations, the ERG therefore considers the company's model to provide the most relevant evidence for the decision problem. The ERG, however, notes that the four identified studies provide an important source for comparison of key structural assumptions and parameter uncertainties.

5.2 ERG's summary and critique of company's submitted economic evaluation

The company presented a *de novo* analysis based on a decision tree (tisagenlecleucel-T treatment group only) and three health state (event free survival, progression disease and death) partitioned

survival model. The ERG notes that the model structure appears similar to the structure used in the economic evaluations identified in the cost-effectiveness review.

A summary of the company's economic evaluation is presented in Table 4, with justifications for key aspects and signposts to the relevant sections of the CS.

Table 4 Overview of the company's economic evaluation

	Approach	Source / Justification	Location in CS
Model	Cost-effectiveness (cost-utility) analysis uses a hybrid approach consisting of a decision tree and partitioned survival analysis approach.	Commonly used modelling framework for oncology. Consistent with the model structure proposed in the York study for a hypothetical CAR T technology with "curative" intent.	Section B.3.2.2.2; p.93
States and events	Hybrid decision model and The model contains 3 states: pre-progression, post-progression and death	The partition approach allows for the modelling of OS and EFS based on the events observed in the clinical trials, ensuring the model is consistent with the clinical data upon which it is based. The approach has been used in previous r/r B-cell ALL submission considered by NICE.[43, 44]	Section B.3.2.2.2; p.96
Comparators	Tisagenlecleucel-T was compared to: • FLA-IDA • Blinatumomab	Consultation with clinical experts suggested that FLA-IDA chemotherapy and blinatumomab are the most appropriate comparators considered. The company noted that blinatumomab is increasingly being used early in the treatment pathway (1st line salvage therapy) potentially making FLA-IDA the primary comparator.	Section B.1.3.2 and Section B3.2.3 p.25 and p102.
Natural History	Based on partitioned survival model. Transitions between states were based on the ELIANA, ENSIGN and B2101J trials (tisagenlecleucel); Jeha *et al* study [7] (FLA-IDA); and, von Stackelberg *et al* [8] trial (blinatumomab).	PFS and OS estimates were modelled independently, with the proportion of progressed patients at each cycle, calculated as the difference between the OS and PFS curves.	Section B.3.3.2; p.104
Treatment effectiveness	Clinical outcomes included EFS and OS. Tisagenlecleucel-T OS and EFS was extrapolated from ELIANA, ENSIGN and B2101J patient level data using a mixture-cure model. FLA-IDA OS extrapolated from Jeha *et al* patient level data using a simple parametric function. EFS was derived from OS by assuming the same ratio between EFS and OS for Tisagenlecleucel-T in the ELIANA, ENSIGN and B2101J trials.	In the absence of an RCT, the uncontrolled comparison was made between the FAS population of ELIANA, ENSIGN and B2101J trials, and historical control data for the comparator therapies. In the base-case analysis naive unadjusted comparisons with historical data. Scenario analysis implementing MAIC adjusted comparisons was also implemented.	Section B.3.3.3 p.122 and 123.

	Approach	Source / Justification	Location in CS
	Blinatumomab OS was extrapolated from von Stackelberg patient level data using a mixture-cure model. EFS was derived from OS by assuming the same ratio between EFS and OS for Tisagenlecleucel-T in the ELIANA, ENSIGN and B2101J trials.	Jeha and von Stackelberg did not collect EFS data, so the EFS estimates for FLA-IDA and Blinatumomab required an assumption on the relationship between EFS and OS. The company assumes in the base-case that this relationship was the same as for tisagenlecleucel-T. It was noted that this assumption is consistent with the approach taken in the mock appraisal. Scenario analysis for blinatumomab was also conducted using relapse free survival data from the von Stackelberg *et al* study.	
HRQoL	Utilities were estimated from published literature on patients will ALL. Utility decrements for adverse events were based on assumptions.	EQ-5D-5L was collected as part of the ELIANA trial, published values were, however, favoured in the base-case analysis. PD values were source from Kelly *et al* (2015) and were generated from CHRI Scores mapped to EQ-5D from paediatric patients who had undergone HSCT. EFS values were drawn from Essig (2012) and were generated from SF-36 scores mapped to HUI2 from patients who had survived for at least 5 years after successfully treated relapse. The Essig (2012) values were also used to estimate long-term survival utilities applied to all patients who survived beyond 5 years in the model. The health state utilities (pre-and post-progression) were assumed the same for both treatment arms. To reflect age-related decline in HRQoL, utility values for LTS were adjusted by applying age related decrements over the modelled time horizon. These were derived from a study by Janssen *et al* (2014).	Section B.3.4.5; p. 128 and 129.

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	Approach	Source / Justification	Location in CS
		Utility decrements were applied for AE's related to treatment, grade 3/4 cytokine release syndrome (tisagenlecleucel-T and Blinatumomab only), non CRS ICU stays (Tisagenlecleucel-T only) and SCT. Treatment related utility decrements were generated from Sung *et al* (2003) and based on time in hospital. The same decrement applied for all treatments. Utility decrements applied for grade 3/4 cytokine release syndrome and non CRS ICU stays (Tisagenlecleucel-T only) were based on an assumption. Duration of CRS was based on the ELIANA trial for both tisagenlecleucel-T and blinatumomab. Duration of non CRS ICU stay was sourced from the ELIANA trial. Utility decrements for SCT were derived from Sung *et al* (2003) and were applied for a period of 1 year.	
Adverse events	Adverse events were included if they were: • Grade 3 or higher AEs occurring in ≥5% of subjects in the ELIANA, ENSIGN and B2101J trials were used estimate AE rates for tisagenlecleucel-T. • Grade 3 or higher AEs occurring in ≥10% of subjects in the Jeha study were used estimate AE rates for FLA-IDA • Grade 3 or higher AEs occurring in ≥5% of subjects in the von Stackelberg study were used estimate AE rates for blinatumomab.	Adverse event rates were drawn from relevant clinical evidence.	Section B.3.5.3; p.148

5.2.1 Model structure

The CS presented a *de novo* cohort cost-effectiveness model to estimate the cost-effectiveness of tisagenlecleucel-T compared with FLA-IDA and blinatumomab in a population of young people with r/r B-cell ALL.

Cost-effectiveness was assessed over a lifetime time horizon of 88 years. The cycle length used in the model was one month, which was considered to be sufficiently granular to accurately capture model costs and outcomes throughout the treatment pathway. A half-cycle correction was applied to costs and QALYs.

The model structure applied is dependent upon whether patients are in the tisagenlecleucel-T arm of the model or receive one of the comparator therapies. This is to account for the manufacturing time required to provide tisagenlecleucel-T. For patients in the tisagenlecleucel-T arm a hybrid modelling approach is taken, combining a decision tree and partitioned survival model structure. The short-term decision tree is used to capture the costs and events prior to the point of infusion tisagenlecleucel-T, and its structure is illustrated in Figure 19. During this manufacturing phase patient may undergo treatment with bridging chemotherapy to stabilise disease and may also receive lymphodepleting chemotherapy, which is recommended prior to infusion with tisagenlecleucel-T.

Figure 19 Model decision tree (presented in the CS Figure 25; pg. 94)

Continue to infusion (P₁)
(Enter tisagenlecleucel arm of partitioned-survival model and accrue costs and QALYs accordingly)

Discontinue due to manufacturer failure or adverse events experienced prior to infusion (P₂)
(Assigned comparator costs and QALYs)

Death event prior to infusion (P₃)
(No entry into partitioned survival model and no further accrual of costs or QALYs beyond those assigned during the decision-tree)

100% of tisagenlecleucel cohort enter decision tree model

Patients selected for treatment with tisagenlecleucel-T can follow one of three possible pathways: i) continue to infusion with tisagenlecleucel-T; ii) discontinue treatment prior to infusion due to either manufacturer failure or AE's; or iii) die prior to infusion. The probability of each these events is drawn from ELIANA, ENSIGN, and B2101J trials, and is summarised in Table 5.

Table 5 Patient proportions in the decision tree by pathway

	Continue to infusion (P1)	Discontinue prior to infusion (P2)	Die prior to infusion (P3)
Proportion of patients who underwent leukapheresis	██%	██%	██%

For patients who survive beyond the initial decision tree phase, a partitioned survival approach is used to model patient outcomes. In a partitioned survival model, transitions between states are not explicitly incorporated into the analysis using probabilities; instead, the proportion of patients in each state is determined by using estimates of survival over time. The modelled health states in the partitioned survival model phase are event-free survival (EFS); progressive disease (PD) and death, (see Figure 20), with the proportion of patients in each heath state determined directly from the EFS and OS survival curves. Survival outcomes for patients who receive infusion with tisagenlecleucel-T are based on survival analyses of patient-level from a pooled analysis of the ELIANA, ENSIGN, B2101J trials. For patients who do not receive tisagenlecleucel-T infusion, either due to failure in manufacture or AEs it is assumed that patients will go on to receive one of the comparator therapies in a 1:1 ratio with survival outcomes based on partition survival model used to model the comparator therapies. These patients are also assumed to receive 50% of the costs of bridging and lymphodepleting chemotherapy. Similarly, patients who die prior to infusion are assumed to incur 50% of the costs of bridging therapy and lymphodepleting chemotherapy.

For patients receiving either of the comparator therapies the decision tree phase of the model is dispensed with, and survival outcomes are determined using partitioned survival model. This uses the same structure as described above.

The model also included an important additional structural assumption, that patients' alive in either the EFS or progressed disease health state at 60 months, will subsequently revert to HRQoL similar to that of the general population and to incur only nominal further costs related to their previous condition.

Figure 20 Partitioned survival modelling approach (presented in the CS Figure 26; pg. 94)
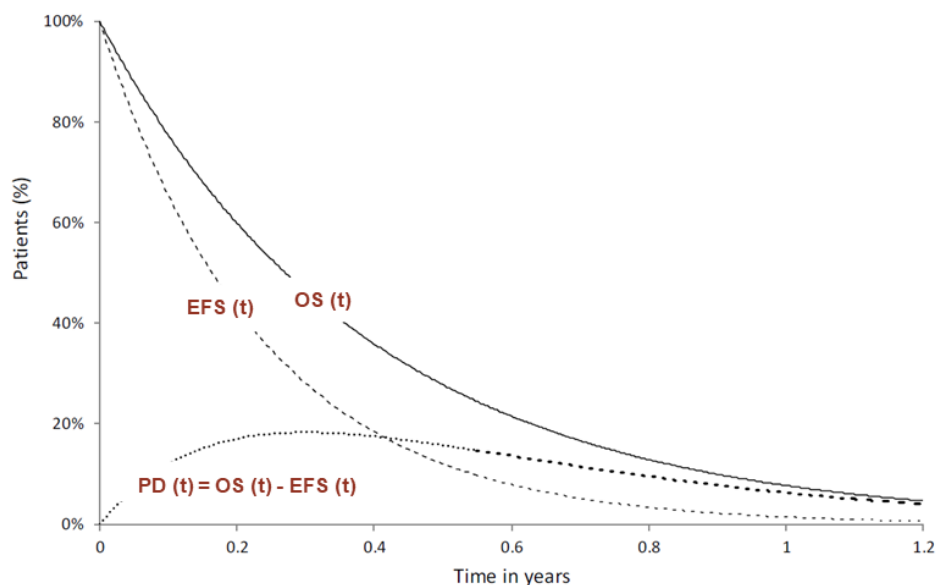
The choice of model structure was justified by the company based on the adoption of a similar model structure in two previous economic evaluations submitted to NICE in which r/r B-cell ALL in adults was evaluated. The addition of the decision tree element to the partition survival model was justified on the basis of a need to capture the costs and benefits associated with patients who, are intended to receive tisagenlecleucel-T and incur the costs associated with pre-treatment, but who do not ultimately receive infusion.

ERG comment

The ERG notes that while the partitioned approach has been adopted in number of previous appraisals and is able is able to accommodate a number of key clinical elements of the treatment of r/r ALL, it assumes that patients cannot improve their health state. This is somewhat problematic in the present context as it means that patients who relapse cannot move back to the remission health state. This would be the case for patients who successfully achieve remission on subsequent lines of therapy. The result of this assumption is that a small proportion of patients continue to remain alive in the relapsed disease health state for a period of up to five years (accruing the QALYs and costs associated with relapse). Exploratory analysis implemented by the ERG, however, suggest that the impact of this assumption is minimal.

With respect to the assumptions made in the decision tree, phase the ERG has a number of concerns.

Firstly, the ERG questions the assumptions made regarding the proportion of patients who do not receive the infusion due to AEs or manufacturing failure. The assumption applied in the company's

base-case analysis implies that ineligibility for infusion will become known on average halfway through the manufacturing period. This, however, seems inconsistent with concept of manufacturing failure and AEs, which in the ERG's view are likely to become known at, or near to the time of infusion. The ERG therefore considers it likely that patients who do not receive infusion due to AEs or manufacturing failure will incur almost all of the costs associated with the provision of bridging chemotherapy and lymphodepleting chemotherapy.

Secondly, the company's base-case analysis assumes that patients who do not receive the infusion due to AEs or manufacturing failure will accrue costs and QALYs in line with the comparator therapies. This is inappropriate as these patients have faced a significant delay in treatment and includes a proportion of patients who do not receive infusion due to AEs. These patients are therefore very likely to be in poorer health than those that go on to receive infusion with tisagenlecleucel-T. This is evidenced by examination of survival data for these patients (Figure 21) which suggests that patients who do not receive infusion have a very poor prognosis with only one patient surviving beyond six months across the three tisagenlecleucel-T trials. The very poor prognosis observed for these patients further suggests that patients who do not receive tisagenlecleucel-T infusion will be unlikely to receive salvage therapy (either FLA-IDA or blinatumomab) due to disease progression. Advice received from the clinical advisor to the ERG suggests that it is likely that the majority of patients will go on to receive (palliative) best supportive care instead of intensive therapy. The ERG, therefore implements scenario analysis in Section 6 exploring alternative assumptions for patients who do not receive tisagenlecleucel-T infusion due to AEs or manufacturing failure.

Figure 21 Kaplan-Meier curve for OS for patients not infused with tisagenlecleucel-T in ELIANA (Clarification response, fig 33)
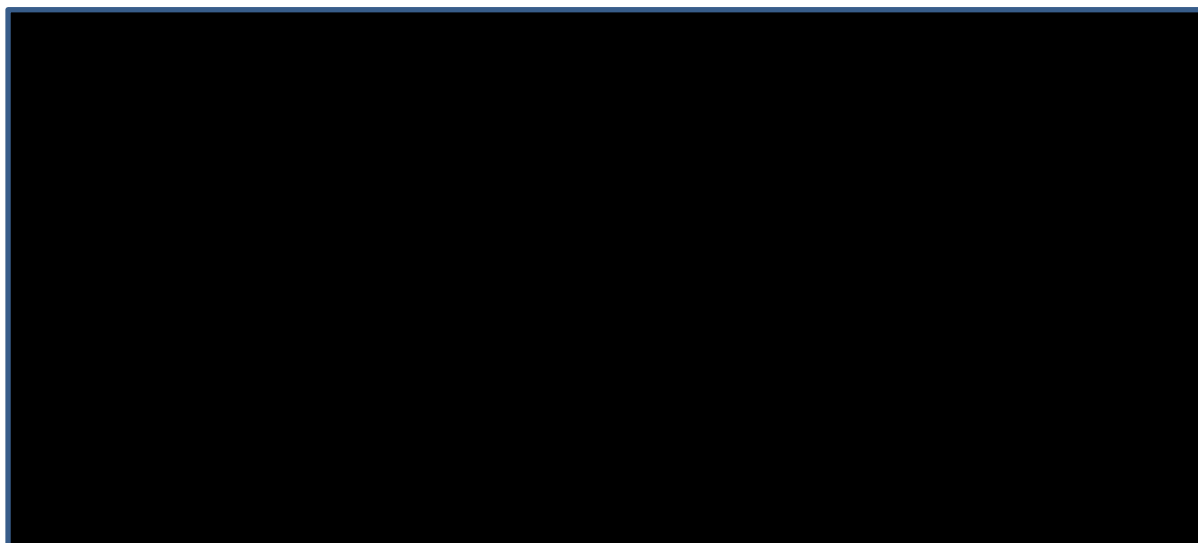
A central feature of the company's model is the concept of cure, and the assumption that a proportion of patients will achieve long-term remission. The company's justification for the application of assuming curative benefits is based on three sources of evidence. The company noted, based on a visual inspection of the KM (EFS and OS) data for tisagenlecleucel-T, a plateau which they consider to be indicative of a proportion of patients achieving cure. In particular, the company highlights the lack of any further deaths after 32 months in the B2101J trial, which represents the study with the longest follow up. The continued persistence tisagenlecleucel-T in the body and its unique mechanism of action, was consistent with the observed OS data and with clinical opinion regarding the effectiveness of tisagenlecleucel-T. The company cited established clinical opinion, and highlights similar assumptions regarding cure made both in the NICE appraisal of blinatumomab and in the York mock appraisal of regenerative medicine[40].

While the ERG considers the points made by the company with respect to the cure assumption compelling, the ERG notes that evidence supporting the long-term effectiveness remains limited, and that the observed plateaus in survival were based on very small numbers of patients at risk; there are only 26 patients observed beyond two years and four beyond three years. The ERG also notes that, clinical experience of tisagenlecleucel-T and other CAR-T cell therapies remains limited, and that tisagenlecleucel-T is very different to existing therapies both in the mechanism of action, which is entirely novel, and has different the product profile - FLA-IDA and blinatumomab are largely used as bridge patients SCT which is well established as a curative therapy. Extrapolation of survival data based on experience with other therapies is therefore subject to additional layers of uncertainty, as the persistence of the long-term CAR-T cell treatment effect is not well characterised or understood. The ERG notes that two alternative scenarios were presented in the York mock appraisal, with alternative product profiles for CAR-T therapy. The first scenario, in line with the company's positioning of tisagenlecleucel-T, assumed CAR-T cell therapies were curative in their own right, and that long-term remission could be achieve using CAR-T cell therapies alone. The second scenario assumed that patients responding to CAR-T therapy would receive SCT to consolidate their remission, i.e. CAR-T is a means of bridging to SCT.

The ERG therefore considers there to be significant uncertainty regarding both the long-term effectiveness of tisagenlecleucel-T, and how it will be used in practice. The clinical advisor to the ERG in particular highlighted substantial remaining uncertainty regarding the positioning and implementation of tisagenlecleucel-T and similar therapies in practice. The ERG does not consider that the uncertainties to which the cure assumption is subject have been fully addressed in the company submission, and discusses this further in Section 4.2.6.

5.2.2 **The company's economic evaluation compared with the NICE reference case checklist**

Table 6 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 6 Comparison of company's economic evaluation with NICE reference case

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	The NICE scope defined comparators as established clinical management without tisagenlecleucel-T at one of the following lines of therapy: • Bone marrow relapse: o Following second or greater bone marrow relapse o Following any bone marrow relapse, within 6 months or less, after allogeneic stem cell transplantation (SCT). • Primary refractory disease: • Philadelphia chromosome positive ALL: o Intolerant to or having failed 2 lines of tyrosine kinase inhibitor (TKI) therapy (or where TKI therapy is contraindicated) o Patients ineligible for allogeneic SCT.	Yes	The comparators in the model included: • FLA-based combination chemotherapy • Blinatumomab The included comparators are consistent with current practice in the UK.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective - costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model uses a lifetime horizon (88 years). No patients are expected to survive beyond this period.

Synthesis of evidence on outcomes	Systematic review	Yes	The source of data for tisagenlecleucel-T was pooled from three studies - ELIANA, ENSIGN and B2101J. The source of data for FLA-IDA and blinatumomab were identified in the company's systematic review.
Outcome measure	QALYs	Yes	Utilities for all three health states in the model were obtained from the literature and derived from EQ-5D and HUI2 data.
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Derived from EQ-5D HUI2 data.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	Time Trade Off
Source of preference data	Representative sample of the public	Yes	
Discount rate	3.5% on costs and health benefits	Yes	Costs and benefits have been discounted at 3.5% per annum.
Equity weighting	No special weighting	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Population

The population defined by the company in the economic evaluation was that expected to be included in the final marketing authorisation, i.e. patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. The primary sources of clinical data used to populate the model were the three tisagenlecleucel-T clinical trials, from which the estimates of the effectiveness of tisagenlecleucel-T were derived, and two phase I/II clinical trials, Jeha *et al* (2006) [7] and von Stackelberg *et al.* (2016) [8], which were respectively used to estimate the efficacy of salvage chemotherapy and blinatumomab. The modelled population drew age, weight, body surface area, and gender characteristics from the three tisagenlecleucel-T clinical trials. These parameters were used to inform long-term mortality and dosing of some chemotherapy agents.

The population considered in the ELIANA, ENSIGN, and B2101J trials comprises of a heterogeneous group of patients that are at different points in the treatment pathway namely, patients refractory to first line-chemotherapy, those refractory to two or more therapies, those who have relapsed two or more times, and patients who have relapsed after a stem cell transplant.

ERG comment

As previously discussed in Section 3.1, the population recruited to the three tisagenlecleucel-T trials is broader than might be expected in NHS practice, due to the inclusion of primary refractory patients, whose outcomes on existing treatments are significantly better than those with second or greater relapse. The ERG considers it uncertain whether primary refractory patients would be considered for tisagenlecleucel-T therapy in UK clinical practice, given the efficacy of current best practice. Furthermore, this group was not included in the Jeha *et al.* study used to estimate the clinical effectiveness of salvage chemotherapy in the company's base-case. In recognition of these concerns, the ERG asked the company to provide a scenario in their model that excluded patients with primary refractory disease. The results of this analysis increase the ICER relative to FLA-IDA from £25,404 to £26,416 per QALY (includes PAS discount), detailed results are presented in Table 18.

While the age distribution of the modelled population is stated to reflect the anticipated license, it was based upon a pooled analysis of the three tisagenlecleucel-T trials that exclude a proportion of the eligible population. Specifically, the ELIANA and ENSIGN trials excluded patients aged <3 years, who make up a significant proportion of the licensed population. The omission of such patients from the evidence base may be important, as subtypes of ALL common to infants (namely KMT2A gene rearrangements) are associated with weaker treatment response and a poor prognosis [45].

5.2.4   Interventions and comparators

The intervention implemented in the model comprises four stages of treatment; leukapheresis, bridging chemotherapy, lymphodepleting chemotherapy, and a single intravenous infusion with tisagenlecleucel-T. As the price of tisagenlecleucel-T manufacture does not vary by dose, the same acquisition cost is applied in the model, regardless of dose received. For patients 50kg and below, the recommended dose was 0.2 to 5.0×10^6 CAR+ viable T-cells/kg, while for those above 50kg this was 0.1 to 2.5×10^8 CAR+ viable T-cells (non-weight-based).

During the manufacturing process, the model assumes ▇▇▇▇ of patients continuing to infusion receive ▇▇▇▇▇▇ bridging chemotherapy in order to stabilise their disease. The bridging chemotherapy regimen incorporated into the economic model was based on advice from UK clinicians, as the drugs and dosing used in the three trials varied according to local practice and

clinician discretion. Drugs and dosages used in the executable model are as follows: allopurinol (100mg/m^2 tid; days 1-5), dexamethasone (6mg/m^2/day; days 1-14, 3mg/m^2/ day; days 15-21), vincristine (1.5mg/m^2 per week), intrathecal methotrexate (12mg/day; days 1 and 8), co-trimoxazole (480mg bid; two consecutive days each week). For patients who discontinued prior to tisagenlecleucel-T infusion due to manufacture failure/AEs, or death, it was assumed that 50% of patients still received the full costs of bridging chemotherapy.

Based on pooled data from the three tisagenlecleucel-T trials, the model assumes that ▮▮▮▮ of patients receive lymphodepleting chemotherapy within one week prior to infusion. The draft SmPC recommends patients are given one of two lymphodepleting chemotherapy regimens which are included in the model accordingly. Regimen 1: Fludarabine (30mg/m^2/day; days 1-4) and cyclophosphamide (500mg/m^2/day; days 1-2). Regimen 2: Cytarabine (500mg/m^2/day; days 1-2) and etoposide (150mg/m^2/day; days 1-3) if patient has experienced a previous grade 4 haemorrhagic cystitis with cyclophosphamide, or has previously been chemo-refractory to cyclophosphamide. Again it was assumed that 50% of those patients who discontinued prior to tisagenlecleucel-T received lymphodepleting therapy.

The most relevant comparators for Tisagenlecleucel-T were elicited by the company from UK clinicians, citing a lack of relevant UK guidelines for treating this group, these were salvage chemotherapy and blinatumomab. The salvage chemotherapy regimen of choice was FLA-IDA, which comprised one cycle of the following: fludarabine (30mg/m^2/day; days 1-5), cytarabine (2mg/m^2/day; days 1-5), idarubicin (8mg/m^{2}day; days 1-3). In the absence of trial data on FLA-IDA in the population of interest, the company opted to use OS data from a study of clofarabine monotherapy as a proxy, see Section 5.2.6 for further discussion.

Dosing of blinatumomab differed in paediatric (derived from von Stackelberg *et al*. 2016 [8]) and adult patients (using blinatumomab SmPC [11]), and was modelled for up to five cycles of treatment in both groups, all cycles were followed by a two week treatment-free period. Cycle 1 in paediatric patients comprised 5μg/m^2/day for days 1-7, followed by 15μg/m^2/day on days 8-28. Cycle 2 and subsequent cycles used 15μg/m^2/day for days 1-28. Adult patients represented 8.3% of the modelled population, and received 9μg/m^2/day for days 1-7, followed by 28μg/m^2/day on days 8-28. Cycles 2+ comprised 28μg/m^2/day for days 1-28. The economic model assumed that patients could also receive a subsequent allogeneic stem cell transplant following treatment.

ERG comment
The ERG considers the intervention as implemented in the economic model to be largely in line with

the anticipated license, however, as discussed in Section 3.2, the dosing and administration schedule used in the B2101J study differed significantly from the two later trials, with ███ of patients receiving more than one dose of tisagenlecleucel-T. Furthermore, ██ of patients received further infusions of the study drug over a month after their first, with many of these occurring up to eight months into the study.

The ERG also considers the assumptions made regarding the duration of bridging therapy subject to considerable uncertainty, as this depends upon the claimed ████ manufacturing time. The ELIANA trial reported a median time from manufacture to infusion of 45 days, therefore bridging therapy may be given for longer in practice. The company provided a report in their clarification response which cited a median throughput time of 23 days on 37 recent batches of tisagenlecleucel-T, so in practice the wait for infusion may be shorter than observed in ELIANA. However, it is still unclear whether the EU manufacturing site will be available for NHS patients, and the time implications associated with the testing and certification of medicinal products imported from third countries (i.e. the USA-based manufacturing facility). There is also uncertainty surrounding the number (████) of patients who did not require bridging therapy; the ERG's clinical advisor suggested that while some patients may not experience significant disease progression within ███████, the existence of this group is less certain over a longer period. The ERG considered that the bridging and lymphodepleting chemotherapy regimens used in the model reflect expected practice in the UK.

With respect to the comparator therapies considered, the ERG's clinical advisor suggested that the relevance of the two comparator regimens varied by response status. There are a wider range of options available to primary refractory patients than suggested by the company, these patients may also be treated according to the NOPHO protocol [30] with the aim of bridging to SCT, while patients aged ≥18 would be more likely to receive blinatumomab before transplant. The ERG also noted that patients aged >18 would also likely receive FLAG-IDA in line with clinical guidelines, i.e. FLA-IDA with the inclusion of granulocyte colony-stimulating factor.

The ERG's clinical advisors suggested that the approach taken to treatment of patients with secondary or greater relapse varies by previous therapies and by treatment centre; however, this is a rapidly changing field, and other drugs such as inotuzumab or daratumumab may also be used. The clinical advisor noted that patients aged 18-25, who made up ███ of the trial populations and comprise around 8.3% of patients in the UK, would be treated with blinatumomab as a first line salvage therapy, which therefore would not be available as an option after second relapse. Both the ERG and the company received clinical advice emphasising that blinatumomab is becoming increasingly common as a first line salvage therapy in paediatric patients. It is therefore likely that FLA-IDA is the

more relevant comparator for patients with two or more relapses (comprising ▮ of the B2101J population; figures unavailable for ELIANA and ENSIGN.

The use of blinatumomab earlier in the treatment pathway also raises the issue of eligibility for later treatment with tisagenlecleucel-T. A key exclusion criterion of the three trials was previous use of an anti-CD19 therapy such as blinatumomab, due to the potential impact upon treatment efficacy. CD19-negative relapse was observed in 22% of those analysed who relapsed in the paediatric blinatumomab trial [46], and as such would gain no benefit from CD19-targeted CAR-T cell therapy. This casts uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients who have previously received blinatumomab. This has implications for current practice that must be resolved, as the availability of tisagenlecleucel-T later in the pathway may affect the willingness of clinicians to use blinatumomab.

In addition the above, the ERG notes that blinatumomab has never been appraised in a paediatric population for this indication, and that in the corresponding adult population the committee's preferred ICER versus salvage chemotherapy was above NICE's usual end-of-life cost-effectiveness threshold. Given that trial results suggest lower efficacy of blinatumomab in children than in adults, the ERG urges caution when comparing tisagenlecleucel-T against a therapy that may not be cost-effective itself.

5.2.5   Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS).[48] The time horizon was described as a lifetime horizon and comprised 88 years (1068 cycles). The ERG considered the time horizon appropriate, as less than 0.00001% patients in the model were expected to remain alive beyond 88 years. However, the long time horizon is driven by the extrapolation and 'cure' assumptions within company's model, which the ERG consider to be subject to significant uncertainties.

A 3.5% discount rate was applied for costs and health benefits, in line with NICE guidance. [47] The company also explored alternative discount rates of 1.5% and 6% in additional scenario analysis.

5.2.6   Treatment effectiveness and extrapolation

As stated in Section 5.2.1, the company used a partitioned survival approach to provide a direct comparison of the timing and rates of relapse, and death. The main effectiveness inputs included in the company's economic model are therefore EFS and OS. For the model base case, OS and EFS survival estimates for tisagenlecleucel-T were drawn from a pooled analysis of the ELIANA, ENSIGN and B2101J trials. To account for the fact that only a proportion of patients go on to receive

infusion the data used was based on the Full analysis set, which included only those patients who received infusion.

The company used the data cut-offs for the ELIANA, ENSIGN and B2101J trials of 31st December 2017, 6th October 2017 and 30th January 2017 respectively. A request for any newer data cuts was made by the ERG at the points for clarification stage, to which the company responded that no newer data cuts are currently available. The company stated that it is expected that a new data cut for the ELIANA trial will become available in July 2018 and in Q3-4 2018 for the B2101J trial.

For the comparator therapies FLA-IDA and blinatumomab data was sourced from the Jeha *et al*. (2006) [7] and von Stackelberg *et al.* (2016)[8] trials. Event-free survival data was not available in either of these studies and therefore EFS was estimated for the comparator therapies by applying the HR between OS and EFS from the three tisagenlecleucel-T trials to the relevant OS curve.

Figure 22 illustrates the KM curves and extrapolated OS curves for tisagenlecleucel-T, FLA-IDA and blinatumomab. The KM data from three tisagenlecleucel-T trials is substantively more mature than that available for either comparator therapy.

Figure 22 Kaplan-Meier and parametric extrapolations of overall survival for tisagenlecleucel-T
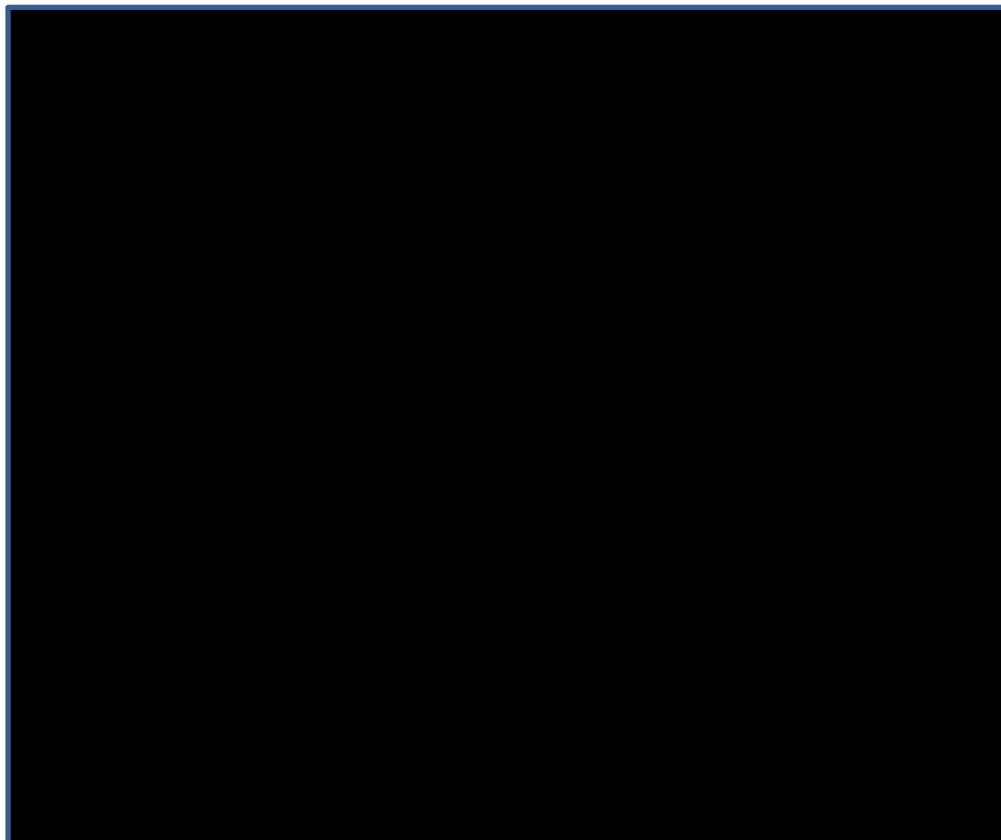
The majority of the survival benefits of tisagenlecleucel-T is due to patients who achieve a long-term cure, and these benefits are largely accumulated during the period of extrapolation. These survival benefits are the primary driver of incremental QALYs and cost-effectiveness in the model. Given this, it is important to consider the assumptions underlying the data and in the extrapolation of survival (EFS and OS).

5.2.6.1 Uncontrolled comparison of treatment effectiveness

As highlighted in Section 4.4.1, a significant area of uncertainty regarding the comparative effectiveness of tisagenlecleucel-T is the use of historical control data to establish the effectiveness of the comparator therapies FLA-IDA and blinatumomab. In particular, concerns were raised regarding the comparability of the population recruited to the three tisagenlecleucel-T trials with the comparator trials. With respect to both salvage chemotherapy and blinatumomab, concerns regarding the comparability of the selected trials are further compounded by the availability of appropriate trial evidence. These issues are discussed in turn for each comparator below.

Blinatumomab

Only one study was identified as relevant: von Stackelberg *et al* (2016) [8]. This was a Phase 1/2 trial of paediatric patients and consisted of a phase 1 dosing escalation study and a phase 2 study in which safety and efficacy were assessed. As described in Section 4.3.1.1, the ERG is satisfied that this is the only relevant trial evaluating blinatumomab in paediatric patients, but highlights a number of concerns regarding how reflective the population recruited to the tisagenlecleucel-T trials. The ERG notes that the population recruited to the von Stackelberg had particular unfavourable characteristics with high proportion of patients considered to be at very high risk based on tumour load, multiple prior relapses and short interval between latest treatment and start of blinatumomab.

The ERG notes that a comparison of the pre-infusion OS data from the three tisagenlecleucel-T trials demonstrates there are substantially fewer deaths observed in the tisagenlecleucel-T trials than on was observed in the von Stackelberg, which may support the assertion that the patients recruited to von Stackelberg were different to those tisagenlecleucel-T trials. The ERG, however, highlights that these difference may be attributable to differences in toxicity profile between blinatumomab the chemotherapy regimens used in the manufacturing period.

The ERG also notes that a comparison of the median survival observed in the von Stackelberg and median survival reported in and the TOWER (age <35 subgroup)[50] and RIALTO[51] trials also suggests that the von Stackelberg had particularly unfavourable characteristics; respective median survival 7.5 months, 9.9 months and 9.8 months.

FLA-IDA

No trials were identified investigating the effectiveness of FLA-IDA in a paediatric population. Instead, the Jeha *et al.* [7] study was selected from a list of six studies investigating alternative chemotherapy regimens including clofarabine monotherapy and clofarabine combination therapy in this population. As noted in Section 4.3.1.2, the ERG has a number of substantive concerns regarding the selection processes used by the company, and does not consider the company to have adequately justified the selection of Jeha *et al.* over other potentially relevant trials.

Examination of potentially relevant factors including comparability of baseline characteristics to the three tisagenlecleucel-T trials, sample size and age of publication (the ERG consider it likely that outcomes have improved over time), however, does not lead to any of the six studies identified in the review to be clearly more appropriate than any other. Indeed, the ERG considers that in general the six trials are a poor match to the tisagenlecleucel-T trials and there reasons to suspect that there are significant prognostic differences between the patients recruited to the tisagenlecleucel-T and those recruited to six of the studies considered by the company. Specifically, the ERG notes that a comparison of the pre-infusion OS data from the three tisagenlecleucel-T trials demonstrates there are substantially fewer deaths observed in the tisagenlecleucel-T trials than any of the six studies considered. While the ERG acknowledge that these differences may be in part explained by differences in the safety profiles of the bridging chemotherapy regimen used in the tisagenlecleucel-T trials and clofarabine in the comparator studies, it does suggest there are other factors underpinning this difference.

Evidence from on the relative effectiveness of chemotherapy (FLAG-IDA, which is used adults with ALL) and blinatumomab in the TOWER trial suggests that the long-term benefits of blinatumomab over salvage chemotherapy are relatively small (Figure 23), and assuming similar relative effectiveness in a paediatric population we would expect to see significant overlap in the KM curves for FLA-IDA and blinatumomab. This would rule out the selected Jeha *et al.* along with a number of the other studies identified and would potentially favour the Hijiya *et al* (2011) study.

Figure 23 Comparison of Jeha, von Stackelberg and Tower trial OS curves
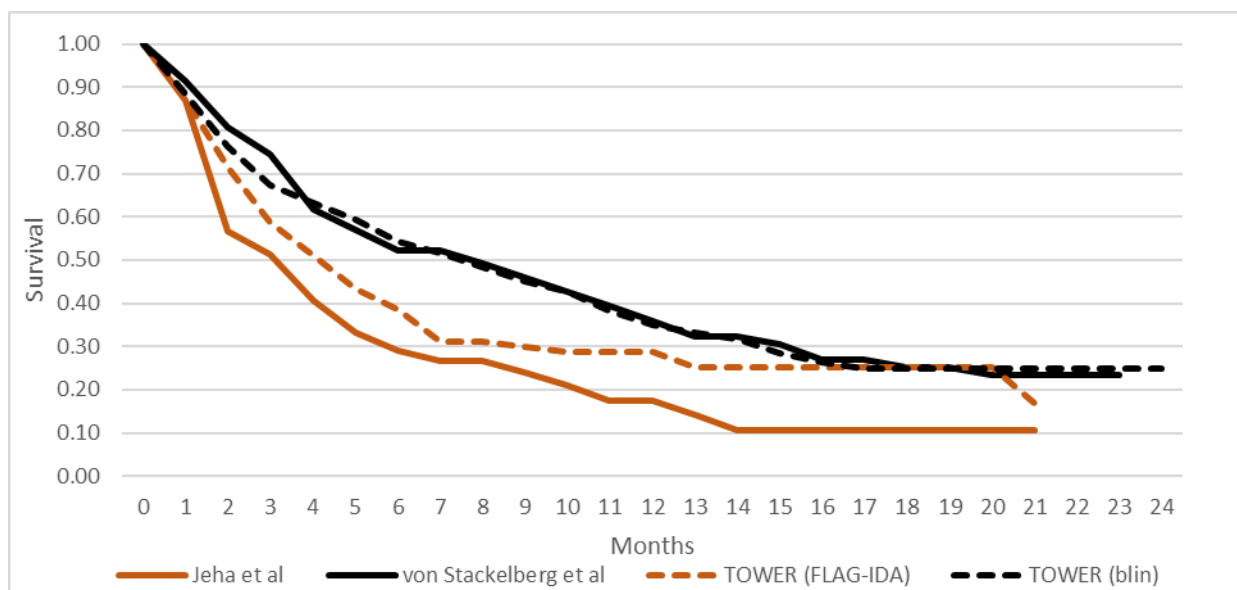
In response to the limitations of the evidence by the company, the ERG performed a limited literature search for further evidence on the prognosis of these patients. These searches identified two relevant studies, both of which were published after the company's searches were undertaken.

The first study identified is Sun *et al.* (2018) [4] which was a retrospective analysis of 325 patients with r/r B-ALL recruited to 24 centres in the US. The patients recruited to the Sun study are largely reflective of the patients expected to receive tisagenlecleucel-T, though limited reporting makes comparisons of baseline characteristics difficult. Further, the survival data presented in this study is limited to those patients who achieve CR. Examination of this data suggests that patients with r/r B-ALL have a substantially better prognosis than is observed in a number of the studies considered by the company including the Jeha *et al* study used in the company base-case.

The second study, Kuhlen *et al* (2017) [12] provides more complete survival data (n=242) for a period of up to 8 years, on patients recruited to two German paediatric ALL trials and who had relapsed following SCT. Kuhlen *et al.* therefore potentially provides a much richer source of data than the studies identified by the company, as it includes a much larger sample and presents significantly more mature survival data. The Kuhlen *et al.* study, however, has a number of limitations. These are described in Table 7 below, and includes a view on the likely direction of bias introduced by each limitation. The majority of these factors would tend to favour tisagenlecleucel-T; however, it is very difficult ascertain the overall net effect of these influences. Despite these limitations, the ERG considers this source of data at least as plausible as the trials identified by the company, with key advantages in terms of the sample size and maturity of data. Importantly, the predicted OS rates align

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well the study by Sun and colleagues identified by the ERG, as a well as several of the trials identified by the company. [22, 23]

Table 7: Limitations of the Kuhlen *et al.* study

Limitation	Direction of bias
Only recruits patients who had received SC; only 57% of participants in the tisagenlecleucel-T have received SCT.	Underestimates OS; patients who relapse following SCT tend to have a worse prognosis than those who have not received a SCT. [4]
A proportion of the patients included (25%) received only palliative care	Underestimates OS; patients eligible for either tisagenlecleucel-T or chemotherapy will have some probability of reaching long-term survival, patients in receipt of palliative care do not.
Includes patients with T-cell ALL (subgroup analysis of EFS reported)	Underestimates OS; patients with T-cell ALL tend to have worse prognosis than patients with B-cell ALL as demonstrated by the reported EFS curves. [12]
Includes patients who have relapsed within 6 months of SCT, these patients would not be eligible for tisagenlecleucel-T. (subgroup analysis of EFS reported)	Underestimates OS; Patients who relapse soon after SCT tend to have a very poor long-term prognosis as demonstrated by the reported EFS curves. [12]
Includes a higher proportion of patients in first relapse than the tisagenlecleucel-T trials (29% vs 23%; data available for B2101J only)	Overestimates OS: the number of relapses is a key prognostic factor and it is established that patients in first relapse do substantially better than patients in second or subsequent relapse. [6]

The ERG therefore presents further scenario analysis incorporating the data from the from the Kuhlen *et al.* (2017) study in Section 6.

5.2.6.2   Overall survival

To extrapolate the available OS for each therapy, a range of approaches were considered by the company. These included use of standard parametric extrapolations (Weibull, log-logistic, lognormal, Gompertz, and generalised gamma); spline models; and mixture cure models. To determine the most appropriate model, the CS states that reference was made to fit statistics (AIC/BIC), visual fit to the observed KM curves, and clinical plausibility of survival estimates.

Tisagenlecleucel

The company fitted a number of standard parametric distributions (Weibull, log-logistic, lognormal, Gompertz, and generalised gamma); spline models; and mixture cure models (Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) to the pooled IPD from the full analysis populations in the ELIANA, ENSIGN and B2101J trials (i.e. infused patients only).

The base-case survival model selected was a mixture-cure model. The company states that the mixture-cure approach was selected for the base-case tisagenlecleucel-T OS analysis due to poor fit of standard parametric functions to capture the change in the hazard function associated with the

observed plateau in tisagenlecleucel-T mortality. Furthermore, the CS justifies the use of a mixture cure approach, highlighting the plateau in the survival curves as indicative of a proportion of patients achieving long-term survival. This is consistent with previous appraisals including TA450 [43], in which the comparator therapy blinatumomab was appraised, and is consistent with expert clinical opinion which suggested that patients who survive beyond 2 to 5 years are essentially cured.

The exponential mixture cure model provided the best statistical fit to the observed data for OS in terms of AIC and BIC (Table 30; CS Page 109) and selected for the base-case analysis. Using an exponential mixture cure model the estimated cure fraction was ▨▨▨. The company noted that this rate is consistent with the pooled tisagenlecleucel-T clinical trial data, which provides follow-up to almost five years (▨▨▨▨), at which point ▨▨ of patients remain alive [52].

Uncertainties surrounding the mixture cure model were addressed by the company using alternative mixture cure models log-logistic and Gompertz models, in which lower cure fractions were estimated. Figure 24 provides a graphical summary of the base case and scenario mixture cure extrapolations.

Figure 24 Extrapolation of tisagenlecleucel-T overall survival using mixture cure models (CS Figure 19, Page 109)
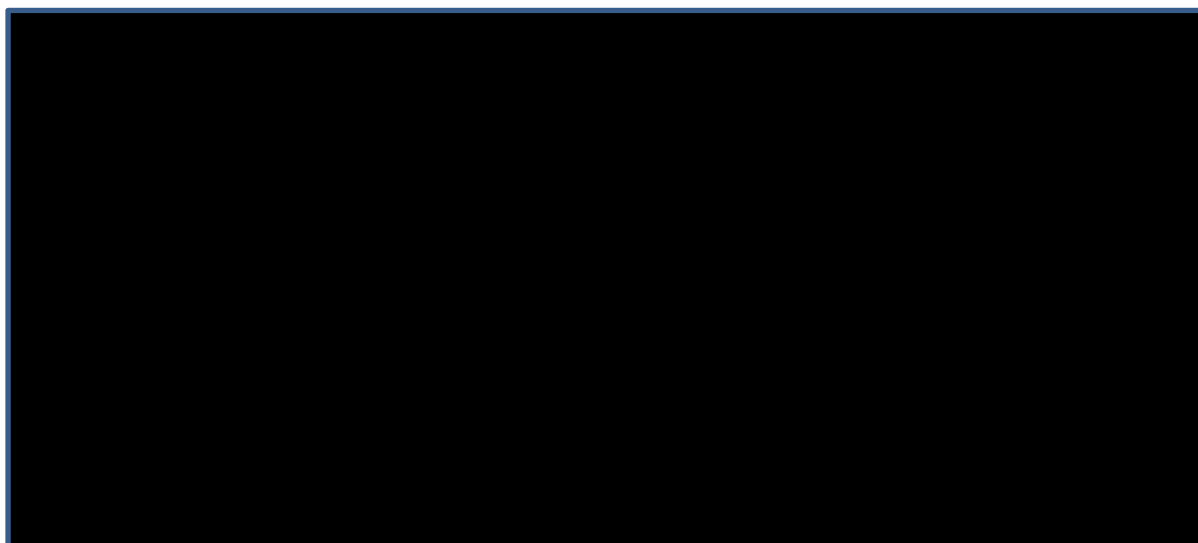
Further scenario analysis was also performed, using an alternative modelling approach. This approach used a single parametric function or spline model to extrapolate OS up to 60 months, thereafter OS was based on general population mortality (age- and gender-matched) to those tisagenlecleucel-T patients with a standardised mortality rate (SMR) applied. Hence, rather than explicitly modelling a 'cure fraction' using a mixture cure approach, it is assumed that those patients who are still alive after a particular time point are effectively 'cured' and have a similar mortality to the general population for the remainder of the model horizon.

ERG Comment

The primary justification put forward by the company for the mixture-cure model approach is its ability to more appropriately capture the plateau in survival implied by the Kaplan-Meier curve. The ERG notes that the observed data for tisagenlecleucel-T was collected over a short follow-up and was based on few patients at risk, compared with the extrapolated period over which the majority of the intervention's QALY gains are accrued. Robust estimation of mixture cure models requires data from studies with long follow-up times that far exceed the anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction [53, 54]. The median follow-up for OS of the study providing the majority of tisagenlecleucel-T survival data ranges between 13.1 months follow up in ELIANA (December 31st 2017 data cut-off date) and ▮▮▮▮▮▮▮ in B2101J (January 30th 2017 data cut-off).

These difficulties in applying the mixture cure model to the current data cuts are exemplified in the significant range in predicted cure fraction reported across the alternative mixture cure models for OS (between ▮▮▮ to ▮▮▮), and the lack of consistency with the cure fractions reported for OS and EFS (see later section). Further, the underlying assumption of cure relies upon on the plausibility of tisagenlecleucel-T inducing long-term curative remission, which is subject to considerable uncertainty give the limited long-term data available and tisagenlecleucel's novel mechanism of action.

Some of the uncertainty surrounding the company's base-case was explored using an alternative approach to extrapolate the available KM data in a separate scenario analysis. This approach assumes that those patients who are still alive after a particular time point are effectively 'cured' and have a similar mortality to the general population for the remainder of the model horizon. Hence, rather than estimating a cure fraction directly, this approach combines the use of a parametric or spline model for a fixed period followed by an adjusted general population mortality rate. The ERG considers that this is a plausible alternative approach to the company base-case and may be more appropriate than the mixture cure model approach given the immaturity in the available survival data.

Considering the plausibility of the company's selected mixture cure model that is based on an exponential function, the ERG notes that is the second most optimistic extrapolation, and importantly the predicted cure fraction exceeds the observed number of EFS events from the three tisagenlecleucel-T trials of ▮▮▮. This suggests that the cured fraction includes patients who relapse, which would seem inconsistent with the basic assumptions of a mixture cure model that the cured fraction represents those patients who achieve long-term response and therefore experience near general population mortality.

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In selecting between the four curves consistent with the EFS KM data, reference to extrapolations made using the simple parametric models and spline models suggest that the Gompertz and log-logistic models are the most plausible models (see approach described below with respect to blinatumomab and Page 113 of the CS). Clinical opinion cited by the company also considered that these extrapolations to be plausible. The ERG, however, cannot completely dismiss the alternative functions (log-normal and generalised gamma) which have very similar statistical fit, particularly given uncertainty regarding the need to consolidate tisagenlecleucel-T response with SCT for patients to achieve long-term remission.

Blinatumomab

Similar to the analysis of tisagenlecleucel-T, the company explored a range of alternative methods to extrapolate OS, including standard parametric distributions, spline models, and mixture cure models. These were fitted to pseudo-IPD generated from the von Stackelberg *et al.* trial [8].

The base-case survival modelling approach selected was a mixture-cure model. The company justified the use of a mixture cure model on the basis that while not a curative therapy, blinatumomab allows patients to receive SCT and to achieve long-term survival, consistent with the application of cure model. The company also highlighted that this is consistent with the approach taken to extrapolating tisagenlecleucel-T OS data, and generated similar projected survival estimates using a simple parametric extrapolation approach with a Gompertz curve fitted (this was the approach taken in the adult appraisal of blinatumomab [43]).

The alternative parametric functions showed similar levels of statistical fit, but resulted in substantial variations in the predicted cure fraction, ranging from 3.9% (generalised gamma) to 21.7 % (Gompertz). The company noted that the immaturity of the OS data available from von Stackelberg and made it difficult to determine the cure fraction, and considered its existence uncertain. To aid in selecting an appropriate curve, the company compared mean OS and undiscounted life years associated with each mixture cure model. Estimates were obtained using a standard parametric model for blinatumomab, under the assumption that patients alive at 5 years are cured and have a mortality risk equal to that of the general population (Table 36; CS Page 117). The exponential, Weibull and Gompertz mixture cure models were excluded as they result in expected survival with blinatumomab that is considerably in excess of predicted survival using a simple parametric approach. The generalised gamma curve was also dismissed because the estimated cure fraction of 3.9% was too low and not clinically plausible. This left the log-normal and log-logistic mixture cure models, which produced similar estimated cure fractions: 11.4% and 12.1% respectively. The company selected to

use the log-normal model on the grounds it had slightly better statistical fit to the log-logistic model (see Table 35; CS Page 116 for AIC and BIC statistics).

Acknowledging the uncertainty in the extrapolation of the blinatumomab OS data, the company also presented a range of scenario analyses using the both simple parametric extrapolation and spline models where patients are assumed cured at 5 years, and alternative mixture cure models.

ERG Comment

The company justify the application of a mixture cure model for blinatumomab by citing consistency with the modelling approach for tisagenlecleucel-T. The ERG acknowledges that a common approach to the analysis of survival data across all three interventions and comparators is desirable as this implies similarity of assumptions for all three interventions. However, as in the case of tisagenlecleucel-T, the application of a mixture cure model to the limited OS data available from the von Stackelberg trial is problematic, with only a short follow-up period relative to the period of extrapolation, which provides the majority of the QALY gains for blinatumomab. Indeed, the follow up in von Stackelberg is shorter than in the tisagenlecleucel-T trials. As previously discussed for tisagenlecleucel-T, this results in a wide range cure fraction estimates; 3.9% to 21.7%, and there is therefore a great deal of uncertainty in the reliability of these long-term extrapolations.

The ERG considers the presentation of the simple parametric functions to allow selection between them to be reasonable, and allows a number of functions to be dismissed. The ERG also considers that the arguments put forward with respect to the clinical plausibility of the exponential, Weibull and Gompertz curves are reasonable and agrees that they produce overly optimistic estimates of the cure fraction given the observed 24 month survival rate of approximately ~23%. Similarly, the cure fraction estimated by the generalised gamma function of 3.8% is implausible given the rates of SCT observed in von Stackelberg (34.9%) and 24 month survival rate. The ERG therefore agrees with the company that the log-normal and log-logistic models represent the most plausible extrapolations. The ERG considers the log-logistic model to match the Gompertz curve used in TA450 more closely, and therefore in contrast with the company the ERG prefers the log-logistic curve over the log-normal curve.

The ERG, however, notes that external validation of predicted OS does demonstrate inconstancies in the estimated survival rates. In the adult appraisal of blinatumomab it was accepted by the committee that 20.9% of patients would achieve cure based on cure point of 4 years. While the assumptions made with respect to the timing of the cure point are more optimistic, this does imply that prognosis of adults receiving blinatumomab is substantially better than in a paediatric population despite almost

identical OS data (see Figure 23), disregarding number-at-risk. As described above, this is inconsistent with clinical experience using chemotherapy-based regimens, where it is established that children tend to have better outcomes.

FLA-IDA

For FLA-IDA, pseudo-IPD was generated from the Jeha *et al.* study which investigated the effectiveness of clofarabine monotherapy, and was used by the company as a proxy for salvage chemotherapy. To extrapolate OS data, the company explored a range of approaches similar to the approach previously described for tisagenlecleucel-T and blinatumomab. This included the fitting of standard parametric distributions, spline models, and mixture cure models. As above, when standard parametric distributions, spline models were fitted, it was assumed that patients alive at five years are cured, and face a mortality risk generated by applying a SMR to age and sex matched general population mortality rates.

The base-case survival modelling approach selected was a standard parametric function with cure assumed at five years. Note that this is in contrast with the company's approach to extrapolating OS for tisagenlecleucel-T and blinatumomab where a mixture cure model was used. The company cited clinical opinion in justification, suggesting that the predicted proportion of patients alive at 5 years based on the best statistically fitting mixture cure models was too high (range 7.2% to 9.4%). The company also highlighted that that clinical expert feedback was clear that few patients in relapse following SCT or in second or later relapse would receive a SCT, and as such few patients would go on to achieve long-term cure.

The generalised gamma standard parametric extrapolation was selected by the company for its base-case analysis, this function was amongst the best fitting models in terms of AIC and BIC (Table 35; CS Page 11). The estimated 5-year survival rate predicted using the mortality generalised gamma model was 3%. The company noted that this was survival rate was consistent with clinical feedback received.

As with the other therapies a range of scenarios analyses were presented by the company, which explored alternative standard parametric functions, spline based models and mixture cure models.

ERG Comment

The ERG considers the modelling approach taken by the company to be inappropriate for a number of reasons.

While the ERG is concerned about the application of mixture cure survival models in the analysis of tisagenlecleucel-T and blinatumomab, consistency in methodology is desirable, and the ERG notes the duration of follow up across the Jeha *et al.* and von Stackelberg *et al.* trials is similar.

The ERG disagrees with the company's assertion that the predicted cure rates are clinically implausible. Advice received by the ERG from its clinical advisor and submissions provided by Leukaemia Care suggest that around 10% of these patients will be alive at 5 years, which is in line with the studies cited previously [4, 12]. This contrasts with the company's base-case, which suggests that just 3% of patients will survival to 5 years. Furthermore, the ERG disagrees with the company assertion that a 50% success rate for SCT is too high; the clinical advisor to the ERG suggested that long-term survival rates following SCT is around 60%.

The estimated 2 to 5 year mortality rate using the company's base case assumptions are far in excess of that observed for other therapies considered; respectively ▮▮▮ and 62% of tisagenlecleucel-T and blinatumomab patients alive at 2 years are alive at 5 years, compared with just 37% of FLA-IDA patients. Over this period substantial differences in the morality rate are not expected between therapies, as any impact of the treatment will have largely dissipated at this point. This is particularly the case when comparing blinatumomab and FLA-IDA, as nearly all patients alive beyond two years will have undergone SCT to consolidate remission and therefore continued remission reflects the effectiveness of SCT rather than induction therapies received.

The ERG highlights the consistency in the cure fractions estimated by the mixture cure models, ranging from 7.2% to 11.5%. This contrasts with the estimates provided for both tisagenlecleucel-T and blinatumomab which vary to a far greater degree, and making the selection of a value far below this range inappropriate given the assumptions for the other treatments.

Evidence from the TOWER trial suggests that the overall survival benefits of blinatumomab relative to FLAG-IDA are relatively small, and we would not expect to observe substantial divergence in the proportion of patients achieving cure between these two therapies.

Therefore, despite concerns about the application of the mixture cure models to both tisagenlecleucel-T and blinatumomab the ERG considers that it more appropriate to apply the mixture cure model to extrapolate the OS data available for FLA-IDA also.

5.2.6.3   Event free survival

Tisagenlecleucel

In common with the approach used for OS, the pooled EFS data from the ELIANA, ENSIGN and B2101J trials were extrapolated using various parametric, spline and mixture cure models, with a mixture-cure model used in the company's base-case. The company justified this choice noting that none of the standard parametric models or spline models provided a good fit to the available KM data, and that this was consistent with the modelling approach used to analyse the OS data.

The company noted that the best fitting mixture cure models were the Weibull, generalised gamma and log-logistic curves, see Table 40 of the CS (Page 122). In selecting between the three curves the company noted that the estimated cure fractions of ▮▮▮ and ▮▮▮ produced by the Weibull, and log-logistic respectively were inconsistent with the cure fraction predicted by the OS models of ▮▮▮▮ The company therefore selected the generalised gamma curve, which estimated the cure fraction as ▮▮▮. A graphical comparison of the extrapolations of PFS using the base case and alternative mixture cure models up to 10 years was also presented (Figure 38; CS Page 122) and is replicated in Figure 25 below.

Figure 25 Extrapolation of tisagenlecleucel-T EFS using mixture cure models (CS Figure 38, Page 122)
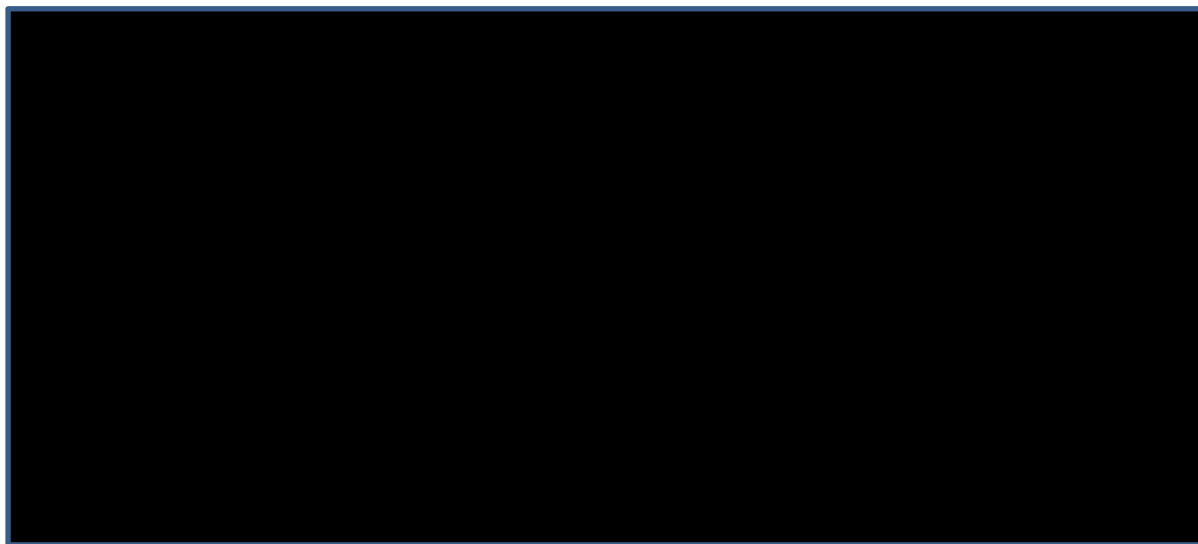
Comparator regimens

Event free survival data were not available for either of the comparator therapies blinatumomab or FLA-IDA, as they were not reported in the von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) studies. The company therefore derived the EFS curves for up to 5 years from the reported OS curves and noted that this approach was taken in the NICE mock appraisal [40]. This was done by applying a

hazard function derived from a UK ALL trial, which reported both OS and EFS data [55]. This approach assumes that the cumulative hazard function for EFS is proportional to the cumulative hazard function for OS. Because EFS was derived from OS, EFS was modelled using the same parametric functions as used to model OS and no separate curve fitting was required.

To explore the uncertainty in the application of this approach the company also present scenario analysis for blinatumomab using RFS data, which was, reported patients who achieved CR. This scenario makes only a marginal difference to the estimated ICER.

ERG Comment
The majority of issues previously raised in relation to the company's approach to OS apply to their analysis of EFS The short follow-up period of the observed data, and the small numbers of patients in the analysis results in uncertainty around how event-free survival data and associated KM curves will develop over time. This is demonstrated by the wide range of cure fractions predicted by the model (██ to ████)

In considering the selected generalised gamma curve, the ERG agrees that this gives the best visual fit to the available KM data and provides the most plausible estimate of the cure fraction given the cure fraction estimated for OS.

The ERG acknowledges the difficulties generated by the fact EFS data were not available for either comparator and is satisfied with the approach taken by the company. The ERG is also reassured by the fact that scenarios based on the RFS data from von Stackelberg have a minimal impact on the ICER, and that pressure tests undertaken by the ERG show that using alternative EFS assumptions has minimal impact on the estimated ICER.

5.2.7 Adverse events

Adverse events from treatment with tisagenlecleucel-T and its comparators were considered in the economic model to capture the associated costs and disutilities. AEs grade 3-4 occurring in 10% or more of subjects in Jeha *et al.,* and 5% or more of subjects in the tisagenlecleucel-T and blinatumomab studies were included in the model. The model also included all B-cell aplasia in patients receiving tisagenlecleucel-T.

The AE rates for tisagenlecleucel-T were derived from the ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017 data cut-off). For blinatumomab, AE rates were source from von Stackelberg *et al.* (2016) and for salvage chemotherapy (FLA-IDA), AE rates were sourced from

Jeha *et al.* (2006). The adverse event rates for each therapy are reported in Table 41 of the CS (Page 124).

The AE rates were applied in the model to estimate associated costs, but not for the estimation of treatment related disutility that was applied as a one-off utility decrement at the first cycle to all patients in the model, see Section 5.2.8 and 5.2.9 respectively for details.

ERG Comment

The ERG is generally satisfied with company's approach to modelling AEs, but notes that the use of Jeha *et al.*, while consistent with the clinical effectiveness data used in the model, is very likely to overestimate the AEs associated with FLA-IDA, as the Jeha *et al*. study evaluates clofarabine, rather than FLA-IDA. As noted previously, clofarabine is rarely used in the UK because of its high toxicity. The ERG therefore undertakes scenario analysis exploring alternative assumptions for the AE rates associated with FLA-IDA by using data from the TOWER trial which compared blinatumomab with a range of chemotherapy regimens including FLAG-IDA in an adult population of r/r B-cell ALL patients.

5.2.8   Health related quality of life

The pivotal trial ELIANA collected HRQoL evidence from trial participants aged 8 years and older using two versions of the EQ-5D tool. The company also undertook a systematic literature review of studies reporting utility values in patients up to 25 years of age with relapsed or refractory B-cell ALL. A brief description of the search strategies was provided in the main body of the submission, with full details provided in Appendix H.

5.2.8.1   Systematic review of utilities and HRQoL

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the National Health Service Economic Evaluations database [NHS EED], and the Health Technology Assessment Database [HTAD]) were searched on 24th November 2017. Conference abstracts and HTA websites were also searched for relevant studies yet to be published.

The structure of the search strategies and sources searched by the company were appropriate for a systematic review of HRQoL studies. Disease terms for r/r B-cell ALL were combined with a set of search terms for utilities or quality of life, and limited to studies published between 2000 and 2017 in the English language.

The systematic search identified 580 records, of which 19 were obtained for full text review. The eligibility criteria were relatively broad (Table 41, Appendix G), and the screening methods used were appropriate. None of the identified studies met the eligibility criteria; consequently, a targeted literature review was conducted, whose results are reported inconsistently between the main submission and appendices. This search identified three utility studies of potential relevance to the decision problem, including a utility study of adults with ALL, the NICE mock appraisal of regenerative therapies (using a paediatric T-cell ALL study), and the US ICER CAR-T review which considered utility values based on young adults with AML.

5.2.8.2   Health state utilities

Health-related quality of life is reflected in the company's model by assigning utility values to the two main health states. Base-case estimates for Progressive disease (PD), and Event-free survival (EFS) were derived from the Kelly *et al.* (2015) study, with a third utility value for long-term survival (LTS) applied all patients who remained alive at 61 months, which was equivalent to the EFS utility.

Table 8 provides a summary of the health state utility values used within the model, and those identified in the literature search.

The company also present a scenario in which the utility values derived from patients in the ELIANA trial are used. Patients aged between 8 and 12 years were assessed using EQ-5D-Y, while the EQ-5D-3L was used for patients aged 13 years and above. There is currently no validated means of converting EQ-5D-Y to a utility score, so utilities were derived solely from the EQ-5D-3L scores of patients aged ≥13 which limited the size and generalisability of this dataset. EQ-5D-3L scores were collected at baseline, Month 1, Month 3, and then every 3 months until Month 24.

Table 8 Summary of utility values applied in model and scenarios

State	Mean utility (SE)		
	Kelly *et al* (2015)	ELIANA	Aristides *et al* (2015)
Progressive Disease	0.75 (0.16)	██████████	0.30 (0.04)
Event-free Survival	0.91 (0.02)	██████████	CR: 0.86 (0.01) CRi: 0.75 (0.02)
Long-term survival*	0.91 (0.02)	██████████	0.86 (0.01)
	Modelled Disutilities	**Source**	
Allo-HSCT (<1 year post)	-0.57	Sung *et al* (2003)	
Chemotherapy (Tisagenlecleucel-T, salvage chemotherapy, blinatumomab)	-0.42	Sung *et al* (2003)	
Cytokine Release Syndrome (Grade 3/4)	-0.91	Assumption (utility=0 during ICU stay)	

The utility estimate applied to patients in the progressive disease state in the model was 0.75, based on the study by Kelly *et al*. (2015) [56], which undertook a systematic review of utility studies and converted SF-36 and CHRI scores to EQ-5D and HUI2. While this study focused on T-cell ALL patients, the utilities were derived from all forms of paediatric ALL. This value is higher than that derived from the ELIANA trial (████), and significantly higher than that reported in the Aristides *et al.* (2015) [57] study (0.30), which used a time trade-off approach to elicit utility values from a representative sample of the general population..

The utility values for event-free survival and long-term survival used by Kelly and colleagues were derived from a Swiss study [58] 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. While the company explains the utility value applied for LTS is based on patients in EFS, this is 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, particularly as the 0.91 value was conditional on >5 years of survival, this study is likely to have excluded the majority of those who initially achieved remission but later relapsed. In Section 6 the ERG presents a scenario using EFS and PD utility values obtained from ELIANA, with the LTS value from Kelly *et al*. to more accurately reflect their respective sources.

To reflect age-related decline in HRQoL, utility values for LTS were adjusted by applying age related decrements over the modelled time horizon. These were derived from a study by Janssen *et al* (2014) [59], which reports estimates of EQ-5D population norms by age elicited from a large sample of the UK population. This approach of age adjusting utilities is commonly applied in models of ALL and AML and the ERG considers these adjustments appropriate.

5.2.8.3   Treatment and adverse event disutilities

Treatment disutilities included in the model were derived from Sung *et al.* (2003) [60], which used physician elicited estimates of disutilities associated with salvage chemotherapy and transplantation. All patients received a utility decrement of -0.42 for the duration of hospitalisation due to treatment, regardless of the regimen received. This disutility was included to reflect a higher likelihood of adverse events suffered at the beginning of treatment with chemotherapy and tisagenlecleucel-T, although this was less applicable to blinatumomab, a scenario analysis performed by the company in which this decrement was removed made little difference to the ICER.

Receipt of allo-HSCT was associated with a one-year utility decrement of -0.57 to capture associated AEs such as GvHD. Sung *et al.* was again the source of this value. The ERG considered this decrement too large, and the duration of its persistence much longer than might realistically be expected, noting the use of tunnel states as a common method for reflecting the improvement in HRQoL over time following SCT, as adverse event frequency and severity, and general health improve. The ERG presents a scenario which applies the Sung *et al.* decrement for 3 months, followed by a smaller decrement of -0.13 for 9 months based on Felder-Puig *et al.* (2006) [61] in Section 6. This improvement in HRQoL over time following SCT is also consistent with other literature on patients with AML[62-64].

Further disutilities were applied to patients who experienced a grade 3/4 cytokine release syndrome (CRS) event. All patients with grade 3/4 CRS were assumed to require ICU admission, with a utility of 0 for the duration of their stay. The ERG note that the company did not apply disutilities associated with lower grade CRS events, nor were disutilities applied for grade 3/4 adverse events other than CRS.

While the treatment-related disutilities applied are likely to encompass AEs experienced during the first month post-infusion, no disutilities are applied for the ▮▮▮▮ of patients experiencing at least one grade 3/4 AE beyond 8 weeks post-infusion in the ELIANA trial. Therefore the model may underestimate the ongoing disutilities in this population which are not otherwise captured in the health

state utilities, particularly when accounting for some of the ▨▨▨ of patients with a grade 3/4 AE within 8 weeks of infusion.

The ERG considers that the two years of utility data derived from the ELIANA trial best reflect the consequences of treatment with tisagenlecleucel-T upon HRQoL, as this data captures treatment and adverse event-related disutility. A scenario is presented in Section 6 which explores the use of these values for two years and excludes the literature-sourced treatment and AE disutilities, after which patients revert to the long-term survival value from Kelly *et al.*

5.2.9 Resources and costs

The CS provided a description of the resource use and costs incurred over time. These included: pre-treatment costs for the tisagenlecleucel-T arm, drug acquisition costs, drug administration costs, follow-up and monitoring costs by health state, hospitalisation and ICU, costs associated with the allo-SCT procedure and subsequent follow-up, costs associated with the treatment of adverse events, and costs related to terminal care that were applied at the end of the patient's life.

The company conducted a systematic literature review (SLR) to identify published evidence regarding the resource use and costs associated with the management of patients aged up to 25 with B-cell ALL. The company found three studies that were considered relevant to the decision problem. The company considered that the resource use reported by these studies were not appropriate for use in this analysis, since they were not conducted from a UK NHS or PSS perspective. As such, the company based resource use in their analysis from previous technology appraisals relevant to the submission [43] [44], and from the ELIANA clinical trial. Where there were no available data, resource use estimates in the company's model were based on recommendations from their clinical experts.

5.2.9.1 Cost of delivering tisagenlecleucel

The total cost of delivering tisagenlecleucel-T therapy was estimated as £314,319.39, based on the list price of tisagenlecleucel-T. The total cost comprised the pre-treatment with lymphodepleting chemotherapy, leukapheresis, bridging chemotherapy, and the infusion of tisagenlecleucel-T. A confidential Patient Access Scheme (PAS) discount of ▨% off the tisagenlecleucel-T list price is currently under discussion with NHS England. With the PAS applied, the total cost of delivering tisagenlecleucel-T therapy was ▨▨▨▨▨▨.

Pre-treatment costs

Pre-treatment costs, consisting of with lymphodepleting chemotherapy, leukapheresis, and bridging chemotherapy costs are summarised in Table 9.

Table 9 Summary of pre-treatment costs

Component	Unit cost	Admin cost	Hospital cost	Source
Leukapheresis	£1,020	-	-	NHS Reference Costs [65]
Bridging chemotherapy	£85.10	£986.07	-	ELIANA, ENSIGN and B2101J, eMIT, BNF, NHS Reference Costs [66] [65]
Lymphodepleting chemotherapy	£122.46	£269.04	£7,101.38	ELIANA, ENSIGN and B2101J, eMIT, NHS Reference Costs [65, 66]

Leukapheresis: All patients receiving tisagenlecleucel-T were assumed to incur the cost of leukapheresis. Costs were based on NHS reference costs (Elective Inpatient, SA43Z Leukapheresis) [65].

Bridging chemotherapy: It was assumed that during the manufacturing period a proportion of patients received bridging chemotherapy to stabilise disease. This proportion was assumed to be ▇▇▇▇ based on a pooled data from the ELIANA, ENSIGN and B2101J trials. Bridging chemotherapy was assumed to be delivered for a period of ▇▇▇▇, which the company cite as the current manufacturing time for tisagenlecleucel-T. Bridging chemotherapy was assumed to consist of the following chemotherapy agents: allopurinol, dexamethasone, vincristine, intrathecal methotrexate and co-trimoxazole. Assumed dosing was estimated from an average dose based on a body surface area of ▇▇▇▇ (source pooled analysis of ELIANA, ENSIGN and B2101J trials). Drug costs associated with each agent were sourced from eMIT and the BNF, see Table 44 of CS (p.134) for details. Associated administration costs were applied to intravenous and intrathecal delivered therapies, with costs applied based on NHS Reference Costs (Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (first administration only) and: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (subsequent administrations) [65].

Lymphodepleting chemotherapy: Prior to infusion with tisagenlecleucel-T, it is recommended that patients undergo lymphodepleting chemotherapy. The proportion of patients receiving bridging chemotherapy was assumed to be ▇▇▇▇ based on data pooled from the ELIANA, ENSIGN and B2101J trials. The economic model included the costs of two alternative regimens of lymphodepleting chemotherapy regimens that are recommended in the draft SmPC, based on fludarabine and cytarabine. Dosing details are reported on p.132 of the CS. It was assumed that ▇▇▇▇ patients would

receive the fludarabine-based regimen and ▇▇▇ the cytarabine based regimen (source ELIANA trial). Drug costs associated with each agent were sourced from eMIT, see Table 44 of CS (p.134) for details. Administration costs were applied for ▇▇▇ of patients for a period of ▇▇▇ days, based on analysis of hospitalisation data from the ELIANA trial. Costs of hospitalisation were based on NHS Reference Costs (weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more (PM40A, PM40B, PM40C). Administration costs were applied to the remaining ▇▇▇ of patients who were assumed to receive lymphodepleting chemotherapy in an outpatient centre and applied for each day of treatment. Costs were based on NHS Reference Costs ("Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance", first administration only, and "Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle", for subsequent administrations) [65].

Infusion with tisagenlecleucel

All patients were assumed to incur an average length of hospitalisation stay of ▇▇▇ days to receive infusion with tisagenlecleucel-T, and an ICU stay of ▇▇▇ days following infusion (both based on median length of stay in the ELIANA trial). The daily cost of hospitalisation and ICU were derived from NHS Reference Costs [65].

Table 10   Summary of costs associated with tisagenlecleucel

Component	Total cost	Assumption / source
Infusion with tisagenlecleucel	▇▇▇	Includes the cost of transportation, manufacture and delivery
Hospitalisation	£19,959.03	Average length of stay ▇▇▇ days (ELIANA), at a cost of £772.11 per day (NHS Reference Costs)
ICU	£2,776.22	Average length of stay ▇▇▇ days (ELIANA), at a cost of £1,559.68 per day (NHS Reference Costs)
Total	▇▇▇	

ERG comment

The ERG considers the company's approach to incorporating the costs of tisagenlecleucel-T treatment and pre-treatment to be generally appropriate.

The ERG, however, notes that the company did not include any costs associated with training for the health professionals in the delivery of tisagenlecleucel-T treatment and its associated care. At the

clarification stage, the ERG requested the provision of more detail on the process of administration, tracking and shipping of apheresis products and the management of severe toxicity with emphasis on any additional resource/cost implications that had not been formally quantified in the model. The company responded that prescribing clinicians, nurses and ICU staff would have to undergo training, to comply with EMA's regulatory requirements, but did not attempt to quantify this element of resource use. In the US, where CAR-T cell is commercially available, all physicians, mid-level providers, pharmacists and nurses who will interact with CAR T-cell patients must undergo FDA mandated training as part of a Risk Evaluation Mitigation Strategy (REMS)[67]. REMS aims to reduce the risks associated with CAR T-cell therapies related adverse events, particularly CRS and neurological events. The regulatory requirements expected to be stipulated by EMA for tisagenlecleucel-T will have the same general purpose and be a determinant of the effectiveness and safety of CAR T-cell therapies.[68]

5.2.9.2 Cost of comparator therapies

The total cost of delivering salvage chemotherapy and blinatumomab was estimated as £17,207.54 and £96,025.01 (based on list price) respectively. These costs are summarised in Table 11.

Table 11 Summary of cost associated with comparator therapies (CS Table 48-50, pg. 141)

Salvage therapy							
Treatment	**Cost per vial**	**Dose**	**Average dose per infusion**	**Vials per infusion**	**Infusions per cycle**	**Total drug cost**	**Total admin cost**
Fludarabine	£23.01 (50 mg)	30 mg/m^2 daily	37.8 mg	1	5	£115.05	£16,214.30
Cytarabine	£6.13 (1000 mg)	2 mg/m^2 daily	2520.0 mg	3	5	£91.95	
Idarubicin	£87.36 (5 mg)	8 mg/m^2 daily	10.08 mg	3	3	£786.24	
Total cost						**£993.24**	**£16,214.30**

Blinatumomab								
Cycle	**Dose**		**Average dose per infusion**		**Vials per infusion**	**Infusions per cycle**	**Distribution of patients per cycle**	**Total drug cost**	**Total admin cost**
	Child	**Adult**	**Child**	**Adult**					
Cycle 1 (days 1–7)	5 mcg/m^2/day	9 mcg /day	5.95	9.00	1.00	7	96%	£54,055.60	£10,749.50
Cycle 1 (days 8–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	21			
Cycle 2 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	31%	£17,749.60	£3,251.91
Cycle 3 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	10%	£5,647.60	£585.15
Cycle 4 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	4%	£2,420.40	£250.78
Cycle 5 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	4%	£2,420.40	£250.78
Total cost								**£82,293.60**	**£13,731.41**

Salvage chemotherapy

Salvage therapy was assumed to be FLA-IDA, which comprises fludarabine, cytarabine and idarubicin. The cost per vial of fludarabine and cytarabine were obtained from eMIT [66], and idarubicin was obtained from the BNF [69].

Dosing for each component of salvage therapy was based on mean body surface area (BSA), which was estimated as ▉▉▉ estimated the average BSA from the ELIANA and ENSIGN trials. The company assumed that vials would not be shared between patients. Patients were assumed to receive one cycle of FLA-Ida. The dosing schedule was based on a protocol from the NHS Network Site Specific Group [70].

It was assumed that FLA-IDA would be administered within a hospital inpatient setting. The company was advised that duration of stay for the treatment cycle would be approximately 3 to 4 weeks, and so applied a daily cost of hospitalisation for 21 days. The hospital cost was estimated as £772.11 per day, and was obtained from NHS Reference Costs (weighted average of elective inpatient excess bed days, paediatric acute lymphoblastic leukaemia) [65].

Blinatumomab

The company estimated the cost of blinatumomab separately for adult and paediatric patients, since they had different dosing schedules. However, each dosing schedule resulted in the same number of vials required, and so adult and paediatric patients had the same total cost.

The unit cost for blinatumomab was £2,017 per 38.5mcg vial [71], and has a confidential PAS. The details of this are provided in the confidential appendix to this report.

The dosing schedule for blinatumomab differed for paediatric and adult patients, and was previously described in Section 5.2.4. Dosing for paediatric patients was based on mean body surface area (BSA), which was estimated as ▉▉▉ for patients under the age of 18, the average BSA from the ELIANA and ENSIGN trials. The company assumed that vials would not be shared between patients.

Patients could receive up to five cycles of blinatumomab. Mean duration of treatment was estimated from treatment exposure data from the von Stackelberg study [8], where the company extracted and applied the proportion of patients completing each cycle of treatment. This study enrolled paediatric patients, and in the absence of any adult-specific data, the company assumed the same duration of treatment for all blinatumomab patients.

As per the SmPC, patients received treatment with blinatumomab as an inpatient in cycle 1 and cycle 2, and received treatment as an outpatient thereafter [11]. Total hospital stay was assumed to be 9 days. In addition, a daily pump set-up cost of £3.89 was applied. The daily hospitalisation cost and outpatient administration cost were estimated from NHS Reference Costs [65].

ERG comment

The ERG consider the company's approach to incorporating the costs of FLA-IDA and blinatumomab to be adequate, but notes two issues.

Firstly, as highlighted in Section 5.2.4, current treatment guidelines in specify that patients aged >18 should receive FLAG-IDA, rather than FLA-IDA i.e. FLA-IDA with the inclusion of granulocyte colony-stimulating factor. The ERG, therefore, considers that the drug acquisition costs associated with chemotherapy should have included the costs of granulocyte colony-stimulating factor for adult patients. This is, however, unlikely to make any appreciable difference to the estimate ICER.

Secondly, while the ERG acknowledges that the duration of blinatumomab was consistent with the source of the effectiveness data (von Stackelberg *et al* (2016)) [8], the ERG was advised that the majority of patients in clinical practice would only receive one cycle of blinatumomab, with only those waiting for SCT given a further cycle. Based on von Stackelberg *et al* (2016), 10% of modelled patients received three or more cycles of blinatumomab, which may lead to an overestimation of total treatment costs. This is explored in Section 6.

5.2.9.3   Monitoring and follow-up

Monitoring and follow-up costs comprised outpatient consultant visits, clinical tests and procedures. These are described in detail in Table 53 and Table 54 of the CS. Unit costs for each were obtained from NHS Reference Costs [65]. A summary of the total costs by health state and by follow-up year, for each treatment arm, is presented in Table 12.

While in the EFS health state for the first five years, monitoring requirements for salvage chemotherapy and blinatumomab were based on those described in the National Comprehensive Cancer Network (NCCN) guideline [72], and the schedule was obtained from the UK Leukaemia and Lymphoma research guideline [73]. Monitoring of tisagenlecleucel-T patients was derived from the ELIANA trial protocol. In the first year of treatment, these patients were associated with a higher monitoring cost, which was mostly due the additional consultant appointments required. For all patients remaining alive in the EFS state after 5 years, the cost of an annual consultant visit was

applied. The cost associated with patients in the PD health state was assumed to be that of the cost of the Year 1 EFS for salvage therapy.

Table 12 Summary of health state follow-up costs per month (CS Table 55, pg. 147)

Health state and year	Tisagenlecleucel	Salvage chemotherapy	Blinatumomab
EFS (year 1)	£439.97	£177.59	£177.59
EFS (year 2)	£77.99	£77.10	£77.10
EFS (year 3–5)	£39.25	£38.55	£38.55
EFS (post 5 years)	£19.02*	£19.02	£19.02
PD	£177.59	£177.59	£177.59
Long-term survivors (EFS and PD)	£19.02	£19.02	£19.02
EFS: event-free survival; PD: progressive disease			
*Note this is incorrectly reported in the CS, table presents corrected value			

ERG comment

The ERG considers the health state costs applied to be reasonable.

5.2.9.4   Allo-SCT costs

It was assumed that a proportion of patients in the model would go on to receive allogenic-SCT, with the rates of SCT sourced from the relevant clinical trial evidence [7, 8]. Table 13 summarises the rate of allo-SCT applied in the company's base-case analysis. These were associated with a cost and a disutility (described in Section 5.2.9 and 5.2.8 respectively).

Table 13 Rates of SCT in the model (CS Table 27, pg. 103)

Intervention	Rate of subsequent allo-SCT	Source
Tisagenlecleucel	▇	Pooled tisagenlecleucel-T clinical trials (ELIANA [31st Dec 2017]; ENSIGN [6th Oct 2017]; B2101J [30th Jan 2017]) [43, 74, 75] [43, 73, 74] [43, 73, 74] [43, 73, 74] [43, 73, 74] [43, 73, 74] (43, 73, 74) (43, 73, 74) (43, 73, 74) (43, 72, 73) [15, 29, 30]
Salvage chemotherapy	16.39%	Jeha *et al.* (2006) [7]
Blinatumomab	34.29%	Von Stackelberg *et al.* (2016) [8]
Allo-SCT, Allogenic stem cell transplant		

The costs associated with allo-SCT comprised the following: stem cell harvesting, the cost of the procedure, and the cost of long-term follow-up. The total cost of allo-SCT was estimated as £116,311.44 (Table 14) and was applied as a one-off cost in the first cycle of the model. The cost of

stem cell harvesting and the allo-SCT procedure were obtained from NHS Reference Costs [65]. The cost of follow-up was obtained from a UK Stem Cell Strategy Oversight Committee Report (2014) [76]. The costs over the follow-up period were weighted for the proportion surviving after the procedure to estimate the total mean follow-up cost per procedure (as illustrated in Table 52 in the CS), and were inflated to 2017 costs using the hospital and community health services (HCHS) index [77].

Table 14 Cost of allo-SCT (CS Table 51, Page 143)

Component	Cost	Source
Stem cell harvesting cost	£3,291.49	NHS Reference Costs
Allo-SCT procedure	£71,694.40	NHS Reference Costs
Allo-SCT follow-up cost	£41,325.56	UK Stem Cell Strategy Oversight Committee (2014)
SCT; stem cell transplant		

ERG comment

The ERG considers the rates of SCT and costs applied to be broadly reasonable, but notes the following points.

As discussed in Section 4.2.6, the trials selected by the company to inform the effectiveness of FLA-IDA are potentially inappropriate and do not reflect patients eligible for treatment with tisagenlecleucel-T. The SCT rates, while consistent with the clinical evidence used in the base-case model, are similarly inappropriate and, therefore, they may not reflect the rate of SCT observed in practice. This is important, as after drug acquisition costs, the cost of SCT is the largest component of the total cost.

Follow costs associated with SCT were obtained from a costing study conducted in the Netherlands between 1994 and 1999 [78]. The SCT process has changed substantially in the intervening period, and that inflating these costs to 2017 may not accurately reflect the current resource use post SCT. There is therefore a degree of uncertainty regarding the total costs associated with SCT.

The total costs of SCT in the CS was applied as a one-off cost to the first-cycle in the model. The cost of SCT follow-up includes costs incurred over a two years period, yet an annual discount rate was not applied for costs in the second year.

5.2.9.5   Adverse event costs

The model incorporated a weighted total AE cost, which was estimated from the unit cost of each event and weighted by the proportion of patients estimated to experience that event over the course of first-line treatment. The costs associated with the treatment of each AE were derived from NHS Reference Costs 2016–2017 [65]. Where an adverse event was not associated with a specific unit cost in NHS Reference Costs, the company assumed equivalence to a similar event. The costs of AEs were applied as a one-off cost in the first cycle of the model. Table 58 in the CS (p.151) reports the AE's rates applied in the economic model and the corresponding unit cost of AEs that were applied in the economic model.

For cytokine release syndrome (CRS) and B-cell aplasia, the company took a more detailed approach to costing, reflecting the fact that these AEs could be associated with substantial resources.

Cytokine release syndrome

CRS events were associated with tisagenlecleucel-T and blinatumomab. Event costs comprised ICU admission and treatment with tocilizumab.

The average length of ICU stay was estimated as being ████████, based on the average length of stay recorded in the ELIANA trial. The company however, noted that feedback from UK clinical experts suggested that this is an overestimate and that, in clinical practice, patients are likely to remain in ICU for only 48 hours. The cost applied for ICU admission was £1,559.68 per day, which was estimated from NHS Reference Costs (weighted average of Paediatric Critical Care (XB01Z-XB07Z, XB09Z)) [65].

Treatment with tocilizumab was assumed to consist of a mean ████████ based on the administration of tocilizumab in the ELIANA trial. Drug acquisition costs per dose of tocilizumab were £579.54 at list price [79]. Tocilizumab has an associated confidential PAS, of which details are provided in the confidential appendix to this report.

Total costs associated with CRS events were £18,029.19, based on the list price of tocilizumab.

B-cell aplasia

B-cell aplasia is common adverse event associate tisagenlecleucel-T affecting 73% of patients, and is associated with continuing persistence of tisagenlecleucel-T cells. It was assumed in the model that patients experiencing B-cell aplasia would receive intravenous immunoglobulin (IVIG). Duration of

IVIG therapy was based on median time to B-cell recovery of 11.4 months sourced from the ELIANA trial (Figure 26).

Figure 26 Kaplan-Meier curve for time to B-cell recovery in patients who achieved CR or CRi in ELIANA (clarification response Figure 28)

The total monthly drug cost of IVIG was calculated based on a dosing schedule obtained from the NICE mock appraisal of regenerative medicine [40] and unit costs obtained from the BNF for Flebogamma [80]. IVIG was assumed to be administered as an outpatient, and the relevant administration cost was obtained from NHS Reference Costs (Chemotherapy, SB12Z, Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance) [65]. The total IVIG cost was estimated as £11,285, and applied as a one-off cost at the beginning of the model.

ERG comment

The ERG notes that CRS represents a common AE affecting ▆ (grade 3/4) of patients receiving tisagenlecleucel-T, and that treatment requires a stay in ICU. The ERG are, therefore, concerned that the provision of tisagenlecleucel-T specialist centres may require that specialist centres hold ICU beds free during the period a patient is considered to be at risk of CRS to ensure availability. This potential represents additional cost not included in the company's base-case model. This issue is explored further in Section 6.

With respect to B-cell aplasia, the ERG notes that KM data on time on time to B-cell recovery remain incomplete and approximately 73% of patients were yet to achieve B-cell recovery 2 years after initial infusion. The company's approach to estimating time to B-cell recovery based on median time to B-

cell recovery is therefore likely to underestimate the mean time to B-cell recovery and consequently total treatment costs associated with B-cell aplasia. To explore this uncertainty, the ERG requested that the company presented scenarios where the duration of IVIG treatment duration was assumed to be 0 months and a lifetime (representing the two extremes). The company considered the lifetime duration of IVIG to be clinically implausible and only presented the 0 months duration scenario. The ERG explores alternative durations for IVIG treatment in Section 6.

Clinical advice received by the ERG also suggested that the company may have overestimated the proportion of patients who will receive IVIG, as it was advised that only patients with recurrent infections associated with more serious grades of B-cell aplasia would be treated with IVIG. At the clarification stage, the ERG requested the company to comment on this point and provide appropriate scenario analysis. The company's response stated that feedback for UK clinical experts suggested that the base-case assumption of all patients experiencing B-cell aplasia was the most appropriate and reasonable assumption and therefore presented no additional scenario analysis. The ERG explores alternative assumptions relating to the proportion of patients receiving IVIG treatment in Section 6.

5.2.9.6 Costs of terminal care

Patients who died in the model prior to five years were assumed to incur a one-time terminal care cost, which was applied during the cycle prior to patient death. The cost of terminal care was assumed to be £7,508.76, based on a weighted average of non-elective inpatient paediatric ALL with length of stay 1 day or more, from NHS Reference Costs [65].

ERG comment

The ERG considers the end of life costs applied in the model appropriate, and similar to those applied in recent appraisals of r/r ALL in adults. The ERG, however, notes that terminal care costs were not applied to patients who die while waiting for infusion with tisagenlecleucel-T. It is unclear whether this was an intentional omission or simply a calculation error. The ERG explores the impact of incorporating end of life costs for these patients in Section 6.

5.2.10 Cost effectiveness results

5.2.10.1 Base case results

The results of the company's deterministic base-case analysis are presented in Table 15 below, these were generated using the inputs and assumptions summarised in Table 59 and Table 60 of the CS.

The base-case results used a discount rate of 3.5% for costs and QALYs over a time horizon of 88 years. When the confidential PAS discount of ▮ is applied, the company found tisagenlecleucel-T was associated with ▮ and ▮ incremental QALYs at an increased cost of ▮ and ▮ versus salvage chemotherapy (FLA-IDA) and blinatumomab respectively. The resulting deterministic ICERs are £25,404 and £18,392 per QALY gained. These results do not include the existing confidential PAS discounts for the comparators, which can be found in confidential Appendix.

Table 15 Company base-case deterministic cost-effectiveness results (inc. tisagenlecleucel-T PAS)

Intervention	Costs (£)	LYG	QALYs	Incremental			ICER
				Costs	LYs	QALYs	
Tisagenlecleucel	▮	▮	▮				
Salvage chemotherapy	▮	▮	▮	▮	▮	▮	£25,404
Blinatumomab	▮	▮	▮	▮	▮	▮	£18,392
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS: patient access scheme.							

The majority of QALY gains for tisagenlecleucel-T were generated from patients in the 'event-free survival' state, which is strongly driven by the cure assumption applied in the model. Table 16 summarises disaggregated QALY gains by health state for each intervention. Graphical traces by treatment arm are presented in Appendix J of the company submission.

Table 16 Summary of QALY gain by health state versus FLA-IDA and blinatumomab

Health state	QALY tisagenlecleucel-T	QALY SC	QALY blinatumomab	Abs. inc. vs SC	% abs. inc.	Abs. inc. vs blinatumomab	% abs. inc.
Event-free Survival	▮	▮	▮	▮	▮	▮	▮
Progressive disease	▮	▮	▮	▮	▮	▮	▮
Treatment & AE Disutilities	▮	▮	▮	▮	▮	▮	▮
Subsequent SCT disutilities	▮	▮	▮	▮	▮	▮	▮
Total	▮	▮	▮	▮	▮	▮	▮
Key: abs. inc., absolute increment, AE, adverse event; SC, salvage chemotherapy; SCT, allogeneic stem cell transplant; tisagenlecleucel-T, tisagenlecleucel-T, QALY, quality-adjusted life year.							

5.2.10.2 Sensitivity analyses

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) using Monte-Carlo simulation with 2,000 iterations. In each iteration, the model drew inputs from defined distributions for selected parameters (CS Table 63, Pages 159-162), and efficacy inputs were modelled using parametric estimates of bootstrapped samples of IPD or pseudo-IPD for OS and EFS extrapolations in the base-case. The probabilistic ICERs were higher than those in the deterministic analysis, as presented in Table 17.

The mean probabilistic ICER was £27,066 per QALY gained versus salvage chemotherapy and £20,046 versus blinatumomab with the confidential PAS discount applied. The probability that tisagenlecleucel-T is the most cost-effective treatment option at a WTP threshold of £30,000 is 65%, and 90% at a threshold of £50,000. The cost-effectiveness acceptability curve for all comparators is provided in Figure 27 below.

Table 17 Company probabilistic cost-effectiveness results (inc tisagenlecleucel-T PAS)

Intervention	Costs	QALYs	Incremental		ICER
			Costs	QALYs	
Tisagenlecleucel	■	■			
Salvage chemotherapy	■	■	■	■	£27,066
Blinatumomab	■	■	■	■	£20,046
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PAS: patient access scheme.					

Figure 27 Cost-effectiveness acceptability curve for all comparators (inc. tisagenlecleucel-T PAS) (CS, executable model)
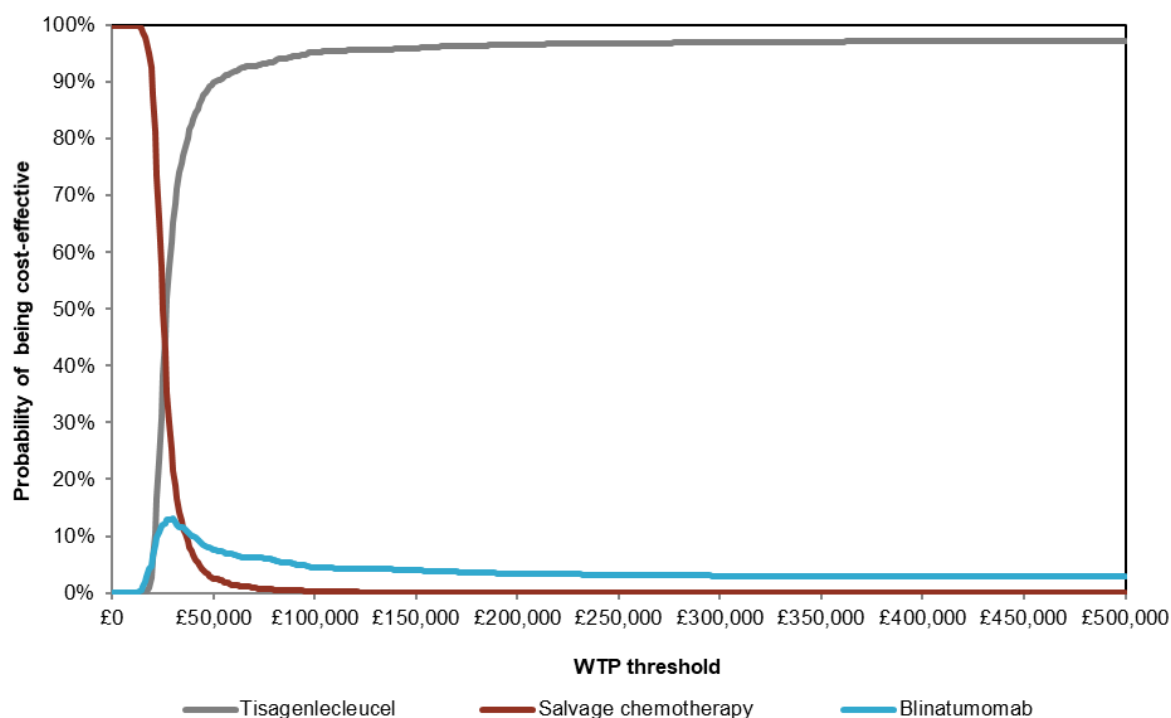
WTP, willingness-to-pay

Compared to the deterministic analysis, the results of the PSA differed significantly in total QALYs, with small differences in costs. The average incremental QALYs gained with tisagenlecleucel-T compared to salvage chemotherapy were ███, which was ███ QALYs fewer than in the deterministic analysis. This was also the case versus blinatumomab, against which tisagenlecleucel-T produced incremental QALYs of ███; ███ fewer QALYs than in the deterministic base-case. These differences are driven primarily by a ███ increase in the total QALYs gained on tisagenlecleucel-T, but the PSA produced estimates ███ and ███ QALYs higher for salvage chemotherapy and blinatumomab respectively. This suggests that the estimates of treatment efficacy used in the deterministic model may not have appropriately captured the uncertainty around these results. The ERG therefore considers the probabilistic ICERs to represent the most appropriate estimates for the purposes of decision making.

Deterministic sensitivity analyses

The company presented a series of deterministic sensitivity analyses (DSA) to assess the impact of varying key model input parameters upon the ICER. The company varied all parameters for which there were single model input values by the upper and lower bounds of the 95% confidence interval, or by ±25% of the mean where 95% CIs were not available. The DSA inputs are summarised in CS

Table 66. Tornado diagrams summarising the twenty most influential parameters as reported by the company are presented in Figure 28 (versus salvage chemotherapy) and Figure 29 (versus blinatumomab). The results indicate that varying the utility values associated with EFS, and the rates of subsequent stem cell transplants had the greatest impact upon the ICER vs salvage chemotherapy, however, these results were relatively robust to changes in the model inputs. The cost of blinatumomab was a key driver of this model's results, which also shared EFS utility and SCT rates as lesser, but influential factors. The DSA did not produce any ICERs greater than £27,000 versus either comparator.

Figure 28 Tornado diagram of the 20 most influential DSA parameters (tisagenlecleucel-T [inc. PAS] vs. FLA-IDA) (CS, Figure 48, Page 170)
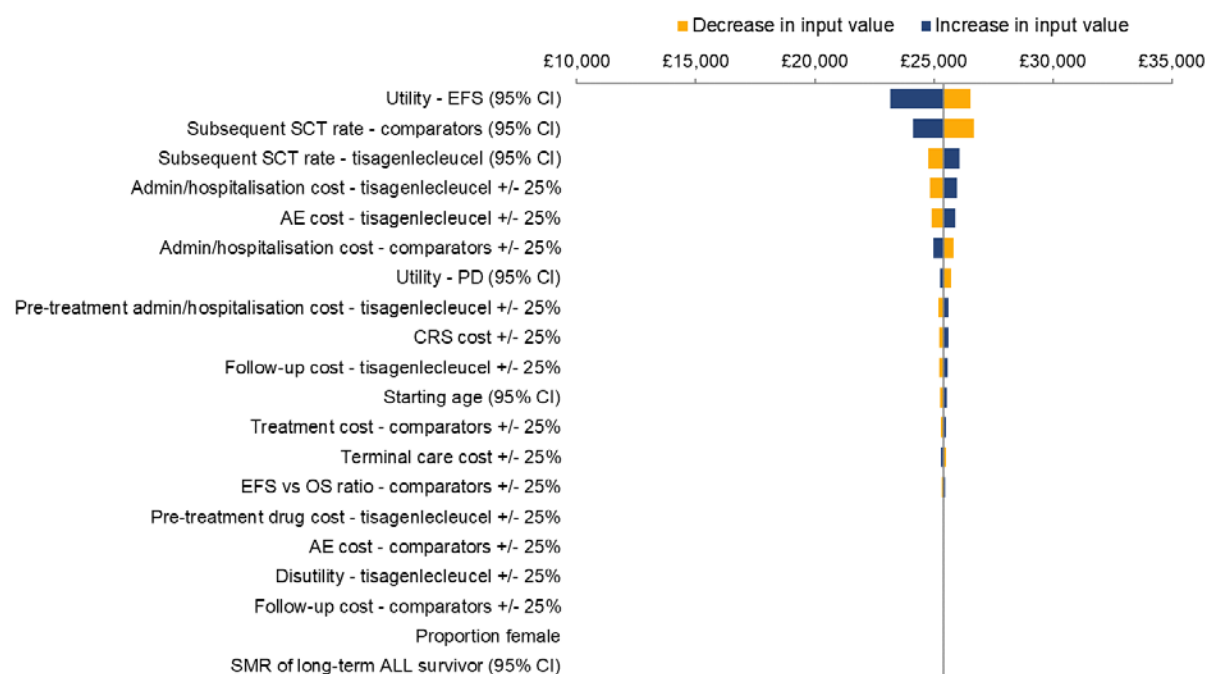
Key: AE, adverse event; CRS, cytokine release syndrome; DSA, deterministic sensitivity analysis; EFS, event-free survival; FLA-IDA, fludarabine, cytarabine and idarubicin; PAS, patient access scheme; PD, relapsed/progressed disease; SCT, stem cell transplant.

Figure 29 Tornado diagram of the 20 most influential DSA parameters (tisagenlecleucel-T [inc. PAS] vs. blinatumomab) (CS, Figure 49, Page 170)
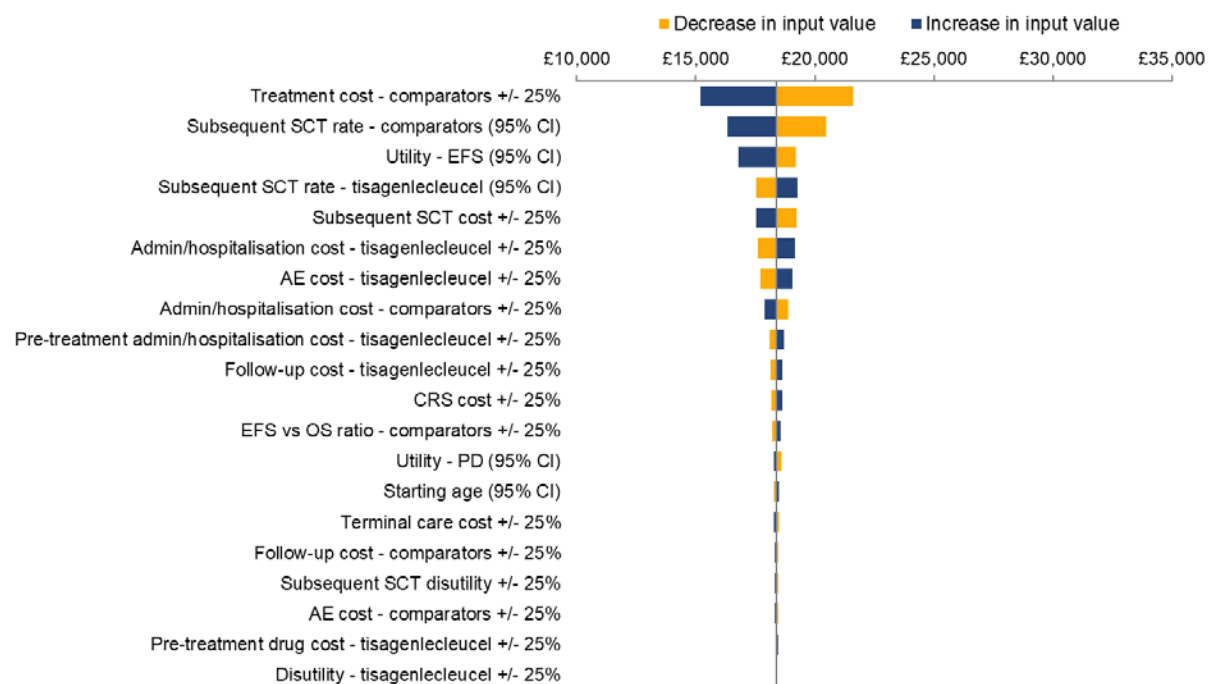
Key: AE, adverse event; CRS, cytokine release syndrome; DSA, deterministic sensitivity analysis; EFS, event-free survival; PAS, patient access scheme; PD, relapsed/progressed disease; SCT, stem cell transplant.

Scenario analysis results

The submission and clarification response included an extensive series of scenario analyses to assess the robustness of the model results and the impact of the assumptions included in the base-case analysis. The results of the scenario analyses performed are presented in Table 18. The results were most sensitive to variations in the time horizon, which is to be expected given the significant upfront costs for tisagenlecleucel-T. The results are relatively insensitive to changes to model inputs and structural assumptions; while some alternative sources of comparator efficacy data increase the ICER by up to £13,500, it remained consistently under £40,000.

Table 18 Scenario analysis results (inc. tisagenlecleucel-T PAS price) (adapted from CS tables 67 to 73, and clarification response)

Scenario	Input	Comparator	Incremental results		
			Costs	QALYs	ICER
Base-case		Salvage Chemotherapy	■	■	**£25,404**
		Blinatumomab	■	■	**£18,392**
Alternative extrapolation: cure model approach	Tisagenlecleucel-T OS extrapolation: log-logistic	Salvage Chemotherapy	■	■	£28,203
		Blinatumomab	■	■	£21,284
	Tisagenlecleucel-T OS extrapolation: Gompertz	Salvage Chemotherapy	■	■	£28,641
		Blinatumomab	■	■	£21,762
	Blinatumomab OS extrapolation: log-logistic	Salvage Chemotherapy	■	■	£25,368
		Blinatumomab	■	■	£19,051
	Blinatumomab EFS extrapolation (von Stackelberg): gen. gamma	Salvage Chemotherapy	■	■	£25,421
		Blinatumomab	■	■	£18,087
Standard parametric extrapolations for all treatments	OS: tisagenlecleucel-T gen. gamma, salvage chemotherapy gen. gamma, blinatumomab gen. gamma; EFS: tisagenlecleucel-T log-logistic, salvage chemotherapy gen. gamma (based on OS), blinatumomab gen. gamma)	Salvage Chemotherapy	■	■	£30,527
		Blinatumomab	■	■	£20,689
Tisagenlecleucel-T overall survival standard parametric survival models	Lognormal	Salvage Chemotherapy	■	■	£31,530
		Blinatumomab	■	■	£21,574
	Gompertz	Salvage Chemotherapy	■	■	£28,942
		Blinatumomab	■	■	£19,321
	Log-logistic	Salvage Chemotherapy	■	■	£33,799
		Blinatumomab	■	■	£23,643
	Weighted by AIC	Salvage Chemotherapy	■	■	£31,758
		Blinatumomab	■	■	£21,778
Blinatumomab overall survival standard parametric survival models	Log-logistic	Salvage Chemotherapy	■	■	£30,637
		Blinatumomab	■	■	£19,134
	Lognormal	Salvage Chemotherapy	■	■	£30,654
		Blinatumomab	■	■	£18,906
	Weighted by AIC	Salvage Chemotherapy	■	■	£30,599
		Blinatumomab	■	■	£19,634
FLA-IDA overall survival standard parametric survival models	Spline single knot	Salvage Chemotherapy	■	■	£30,302
		Blinatumomab	■	■	£20,700
	Weighted by AIC	Salvage Chemotherapy	■	■	£29,864
		Blinatumomab	■	■	£20,722
Alternative cure points	2 years	Salvage Chemotherapy	■	■	£23,842
		Blinatumomab	■	■	£18,321

	3 years	Salvage Chemotherapy	▮	▮	£26,229
		Blinatumomab	▮	▮	£18,890
	4 years	Salvage Chemotherapy	▮	▮	£28,487
		Blinatumomab	▮	▮	£19,771
Source of long-term standardised mortality ratio	Armstrong 2016[81]	Salvage Chemotherapy	▮	▮	£32,271
		Blinatumomab	▮	▮	£21,874
	Bhatia 2005[82]	Salvage Chemotherapy	▮	▮	£29,554
		Blinatumomab	▮	▮	£20,030
	Socié 1999[83]	Salvage Chemotherapy	▮	▮	£32,593
		Blinatumomab	▮	▮	£22,093
Tisagenlecleucel-T efficacy data source	ELIANA only (OS Gompertz, EFS exponential)	Salvage Chemotherapy	▮	▮	£18,426
		Blinatumomab	▮	▮	£12,296
	ELIANA and ENSIGN only (OS Gompertz, EFS exponential)	Salvage Chemotherapy	▮	▮	£20,407
		Blinatumomab	▮	▮	£13,805
Salvage chemotherapy efficacy data source	von Stackelberg 2011 [84] (OS gen. gamma, EFS based on OS)	Salvage Chemotherapy	▮	▮	£20,890
		Blinatumomab	▮	▮	£18,737
	Kantarjian 2017 [50] (OS spline single knot, EFS log-logistic)	Salvage Chemotherapy	▮	▮	£26,743
		Blinatumomab	▮	▮	£18,344
	Hijiya 2011[23] (OS weighted using AIC, EFS based on OS	Salvage Chemotherapy	▮	▮	£27,615
		Blinatumomab	▮	▮	£18,361
Blinatumomab efficacy data source	RIALTO EFS and OS (OS log-logistic, EFS spline single knot)	Salvage Chemotherapy	▮	▮	£25,732
		Blinatumomab	▮	▮	£14,067
	RIALTO OS (OS log-logistic, EFS based on OS)	Salvage Chemotherapy	▮	▮	£25,732
		Blinatumomab	▮	▮	£14,059
MAIC population for Tisagenlecleucel	Standard parametric model: OS Gompertz, EFS log-logistic	Salvage Chemotherapy	▮	▮	£27,833
		Blinatumomab	▮	▮	£15,203
Utility values	ELIANA utilities	Salvage Chemotherapy	▮	▮	£28,937
		Blinatumomab	▮	▮	£20,907
	No treatment disutility for blinatumomab	Salvage Chemotherapy	▮	▮	£25,403
		Blinatumomab	▮	▮	£18,423
Time horizons and discount rates	10-year time horizon	Salvage Chemotherapy	▮	▮	£71,663
		Blinatumomab	▮	▮	£53,913
	20-year time horizon	Salvage Chemotherapy	▮	▮	£43,397
		Blinatumomab	▮	▮	£31,813
	40-year time horizon	Salvage Chemotherapy	▮	▮	£29,835
		Blinatumomab	▮	▮	£21,600
	1.5% discount rate	Salvage Chemotherapy	▮	▮	£16,202
		Blinatumomab	▮	▮	£11,747
	6% discount rate	Salvage Chemotherapy	▮	▮	£37,971
		Blinatumomab	▮	▮	£27,683
Costs	Vial sharing	Salvage Chemotherapy	▮	▮	£25,110

		Blinatumomab	■	■	£25,605
	AE costs set to zero for all therapies	Salvage Chemotherapy	■	■	£23,560
		Blinatumomab	■	■	£15,930
	Tocilizumab PAS discount 20%	Salvage Chemotherapy	■	■	£25,398
		Blinatumomab	■	■	£18,385
Decision tree scenarios	100% of patients receive tisagenlecleucel-T infusion	Salvage Chemotherapy	■	■	£25,186
		Blinatumomab	■	■	£19,575
	100% of patients receive tisagenlecleucel-T and all pre-treatment costs	Salvage Chemotherapy	■	■	£25,247
		Blinatumomab	■	■	£19,654
Responses to clarification questions					
Question B-1: Exclude patients with primary refractory disease	Mixture cure model approach: OS loglogistic, EFS Gompertz	Salvage Chemotherapy	■	■	£26,416
		Blinatumomab	■	■	£19,407
Question B-2: Salvage chemotherapy alternative efficacy data sources	Hijaya 2011 standard parametric model: OS weighted using AIC, EFS based on OS)	Salvage Chemotherapy	■	■	£27,615
		Blinatumomab	■	■	£18,361
	Hijaya 2011 mixture cure model: OS log-logistic, EFS based on OS)	Salvage Chemotherapy	■	■	£38,883
		Blinatumomab	■	■	£18,038
	Locatelli 2009 [9] standard parametric model: OS lognormal, EFS from OS	Salvage Chemotherapy	■	■	£23,371
		Blinatumomab	■	■	£18,544
	Locatelli 2009 mixture cure model OS lognormal, EFS from OS	Salvage Chemotherapy	■	■	£28,590
		Blinatumomab	■	■	£18,277
Question B-9: IVIG treatment duration	0 months	Salvage Chemotherapy	■	■	£24,359
		Blinatumomab	■	■	£16,956
Question B-12: Cytokine release syndrome treatment costs	CRS events grade 1-4 incur treatment costs	Salvage Chemotherapy	■	■	£26,161
		Blinatumomab	■	■	£19,420

5.2.11 Model validation and face validity check

The company states that clinician input was sought on the approach and inputs used in the economic modelling. This included validation of the following model inputs: resource use, AE rates, proportion of patients receiving SCT, utility values, post cure mortality, and eligible patient characteristics. Comparisons between the clinical trial and undiscounted median and mean EFS (where available) and OS predicted by the model and source data were presented in the CS appendices.

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the carrying out a series of black-box tests, to evaluate the internal validity of the model. These black-box tests examined the internal logic of the model, as well checking the predictive validity of the parameter inputs (e.g., that increasing the effectiveness of the treatment lowers cost-effectiveness). Further to this, the code of the model was examined for potential errors, which included tracking how the parameters fed into the model and an examination of the main calculation sheets, with a view to understanding how the QALYs and costs were accumulated in the model. This review identified a small a number of calculation errors related to the application of mortality in the model. These errors were corrected by the ERG and the results for the corrected model are presented in Section 6.

The ERG also notes that in the probabilistic sensitivity analysis, uncertainty in the effectiveness inputs (OS and EFS) was implemented using a bootstrapping approach (where sample data is resampled) as opposed to the more standard approach of assigning a distribution to parameter inputs. The ERG is concerned about the transparency of this approach as few details were included in the CS and the samples drawn upon are hard coded into the executable model making validation impossible. This is particularly important as OS is a key driver of cost-effectiveness and it does appear that there is some divergence in the deterministic and probabilistic results.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic model and analysis to meet the requirements of the NICE reference case. However, there were a number of concerns that contributed to uncertainty in the cost-effectiveness results. These included the following:

1) The assumption of cure and long-term remission on tisagenlecleucel-T

The ERG notes that significant uncertainties remain regarding the long-term extrapolation of OS data for tisagenlecleucel-T and the use of mixture-cure models. The plateau in OS data considered by the company as indicative of cure is based on very small numbers of patients at risk; there are only between 4 - 7 patients alive beyond three years across the three tisagenlecleucel-T trials, while cure is not typically considered until 4-5 years. The ERG also notes the limited experience of CAR-T cell

therapies, and that its novel mechanism of action means the implications of a ~18 month OS plateau cannot be considered analogous to that following SCT, which has been proven to be curative over several decades. Extrapolation of survival data based on experience with other therapies is therefore subject to additional layers of uncertainty, as the persistence of a long-term CAR-T cell treatment effect is not well characterised. Despite these concerns, the ERG concluded that a curative approach to the model was sufficiently clinically plausible for the purposes of decision-making.

2) *Uncertainty surrounding the extrapolation of OS data for tisagenlecleucel-T and comparators*

The application of mixture cure models was inconsistent and potentially inappropriate, given the uncertainty around the long-term effects of tisagenlecleucel-T. The cure fraction estimates generated using mixture cure models for tisagenlecleucel-T varied between ███ and ████, which in itself indicates inadequate data. The company's base case used the second most optimistic cure fraction of ███, in excess of the observed proportion in long-term EFS of ████, which is not clinically plausible.

While the ERG prefers consistency in the curve-fitting approach, the application of a cure model to blinatumomab was also inappropriate, again indicated by the uncertainty in cure fraction estimates (3.9 – 21.7%). The ERG preferred the log-logistic extrapolation over the company's preferred log-normal, as this matched the Gompertz curve used in TA450 more closely. The ERG notes the significant difference between the cure fraction selected by the company of 11.4%, and the ~21% used in TA450; implying prognosis is significantly better in adults than in paediatric patients, despite a near identical OS KM curve.

The ERG considered the fitting of a parametric curve to clofarabine OS data inappropriate, given the use of mixture cure models for the other arms. While cure models were discarded by the company on the grounds of clinical plausibility of estimates, the ERG highlights that these estimated cure fractions (7.2 – 9.4%) are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable, and notes the similarity of long-term OS between blinatumomab and FLAG-IDA in the TOWER trial.

3) *Uncertainties surrounding the relevance of selected comparators and potential impact of blinatumomab on eligibility to receive tisagenlecleucel*

The ERG highlights the uncertainty regarding the treatment of patients with 2+ relapses in the NHS. Firstly, 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 means this population would not be eligible for blinatumomab again after a second relapse, as considered in this appraisal. Clinical advice to the ERG and company suggests this is increasingly becoming the case in paediatric patients; as blinatumomab is used earlier in the treatment pathway, it may be that FLA-IDA is the most relevant comparator for patients with two or more relapses. However, the ERG notes that this is a rapidly evolving field, and other drugs such as inotuzumab and daratumumab are also being used at this point in the treatment pathway.

The ERG also considers the impact of blinatumomab use earlier in the treatment pathway to raise the issue of eligibility for tisagenlecleucel-T after 2+ relapses. A key exclusion criterion of the three tisagenlecleucel-T trials was the previous use of an anti-CD19 therapy such as blinatumomab, 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. This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy. The ERG considers that CD19 expression would need to be quantified before patients could be considered for treatment with tisagenlecleucel-T, as patients with weak or no expression of CD19 would gain little to no benefit from this treatment.

4) *Identification and selection of appropriate comparator data source*

The ERG does not consider the company to have adequately justified their selection of Jeha *et al*. (2006), and does not consider this trial an appropriate basis for informing efficacy estimates for salvage chemotherapy. The is Jeha *et al* study suggests patients receiving salvage chemotherapy have a substantively worse prognosis than those receiving blinatumomab; however, the TOWER study upon which the approval of blinatumomab in adults was based, suggests the long-term benefits over salvage chemotherapy (FLAG-IDA) are relatively small. The ERG suspects there were significant prognostic differences between patients recruited to the tisagenlecleucel-T trials, and those recruited to the studies of clofarabine-based regimens considered by the company, which appears to be corroborated by comparison with pre-infusion OS data from ELIANA and ENSIGN. The ERG identified two recently published studies on 325 and 242 patients, with more mature survival data,

considering these at least as plausible as the clofarabine trials as a source of data on long-term survival of salvage chemotherapy patients.

5) Uncertainties surrounding the modelling of patients who did not receive infusion

The ERG had several concerns regarding the modelling of patients who discontinued prior to infusion. These issues stem from the manufacturing time of tisagenlecleucel-T, around which there is still unresolved uncertainty, and note that delays in manufacturing may preclude the option for alternative potentially curative therapies. The company's model assumes patients who do not receive infusion due to manufacturing failure or AEs will accrue costs and QALYs of the comparator therapies, with many patients in EFS; however, trial data from ELIANA and ENSIGN suggests all non-infused patients die before 6 months, with none achieving remission. The model also likely underestimates costs associated with bridging chemotherapy and lymphodepleting chemotherapy, as non-infused patients incur only 50% of these costs, the ERG believes AEs and manufacturing failure will be weighted towards the end of the manufacturing period.

6) Uncertainty surrounding broader infrastructure and training requirements

Given the complexity of this intervention and patient care needs, the lack of a clear service specification for the production, provision, and administration of tisagenlecleucel-T on the NHS, the ERG considers that there are important remaining uncertainties regarding the quantification of additional resource and investment requirements for the NHS. Particular consideration should be given to additional infrastructure requirements that have not been captured in the presented analyses. The ERG highlight particular uncertainty surrounding additional paediatric ICU beds capacity may need to be made available (even if not used) to ensure that patients receiving tisagenlecleucel-T can be guaranteed access to appropriate services if and when required, without adversely affecting the provision of care to other patients.

The ERG also notes that the cost of additional training that may be required is not considered in this model.

1) Treatment of B-cell aplasia

B-cell aplasia is common adverse event associate tisagenlecleucel-T effecting 73% of patients, and is associated with continuing persistence of tisagenlecleucel-T cells. It was assumed in the model that patients experiencing B-cell aplasia would receive intravenous immunoglobulin (IVIG) with duration of IVG based n median time to B-cell recovery of 11.4 months sourced from the ELIANA trial. The

ERG, however, notes that that KM data on time to B-cell recovery remain incomplete and approximately ▮ of patients who achieved CR were yet to achieve B-cell recovery 2 years after initial infusion. This suggests that the company's approach to estimating time to B-cell recovery is likely to underestimate the mean time to B-cell recovery and consequently total treatment costs associated with B-cell aplasia. Clinical advice received by the ERG also suggests that the company may have overestimated the proportion of patients who will receive IVIG, as it was suggested that only patients with recurrent infections associated with more serious grades of B-cell aplasia would be treated with IVIG.

2) *Treatment and health-state disutilities on tisagenlecleucel-T*

All utility values used in the model were derived from external sources, despite the availability of HRQoL data from the ELIANA trial. As treatment disutilities associated with tisagenlecleucel-T treatment and adverse events are unknown, the ERG considered it more appropriate to use the trial-derived utilities for patients in EFS and PD up to two years, as this data incorporates disutilities associated with treatment and longer-term AEs.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

The following sections provide details of the ERG's additional analyses used to explore the key issues and uncertainties raised in the review and critique of the company's cost-effectiveness presented in Section 6.1 Section 6.2 describes the impact of errors identified in the ERG's validation of the company's executable model. Section 6.3 presents the results of a series of exploratory analyses, examining the impact of alternative assumptions upon the robustness of the cost-effectiveness results, based on uncertainties identified by the ERG. The analyses presented in Section 6.3 focus on the following issues:

- Alternative assumptions around the prognosis and treatment of non-infused patients in the tisagenlecleucel-T arm regarding their OS, and their associated costs and QALYs,
- Methods used to analyse extrapolate OS data,
- The source of clinical data used to estimate the survival of patients on salvage chemotherapy
- B-cell aplasia duration and costs of IVIG,
- Post-SCT quality of life and anticipated SCT uptake in practice,
- Number of lines of blinatumomab treatment modelled,
- The health state utilities used in the model.

In Section 6.4 the ERG presents an alternative base-case based on a combination of the exploratory analyses presented in Section 6.3, which the ERG considers to be more reflective of the cost-effectiveness of tisagenlecleucel-T. Section 6.6 presents a brief conclusion summarising the ERG's additional analyses.

Due to time constraints, ICERs based on the deterministic analysis are presented throughout this section with the exception of the ERG alternative base-case. The results in this section are presented with the confidential PAS for tisagenlecleucel-T. Results with the application of PAS discounts for blinatumomab and tocilizumab are provided in the confidential appendix that accompanies the ERG's report.

6.2 ERG corrections and adjustments to the company's base case model

An error in the company's executable model was identified by the ERG in the company model regarding the application of long-term mortality in the mixture cure models. In the company's model,

mortality in each period was estimated as the higher of that predicted by the mixture cure model and (sex and age adjusted) general population mortality with a SMR applied. This mortality rate was then applied to the proportion of patients estimated to be alive according to the mixture cure modelling. This meant that when the modelled OS could not deviate from the curve estimated by the mixture cure model even when general population mortality based values were being used. The ERG addressed this issue by applying the appropriate morality rate to the estimated proportion of patients predicted to be alive in the last period. The impact of the ERG's correction was to reduce the number of QALYs in the tisagenlecleucel-T and the blinatumomab arms, leading to an increase in both ICERs. Note this correction did not affect the base-case predicted costs and QALYs for salvage therapy as a mixture cure model was not used.

Table 19 ERG corrections to company's model (tisagenlecleucel-T PAS price)

Comparator	Costs	QALYs	Incremental results			Change in ICER
			Costs	QALYs	ICER	
Company's base-case results						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£25,404	-
Blinatumomab	███	██	███	██	£18,392	-
Company's base-case results including ERG's mortality calculation correction						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£28,806	+£3,402
Blinatumomab	███	██	███	██	£20,864	+£2,471
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life year; PAS, patient access scheme						

6.3 Additional ERG analyses

6.3.1 Modelling patients who did not receive infusion with tisagenlecleucel

As discussed in Section 5.2.1 the ERG had concerns about the modelling of patients who were not successfully infused with tisagenlecleucel-T due to death, AEs, or manufacturing failure.

Patients who died before infusion did not incur terminal care costs; the first scenario in Table 20 below explores the impact of inclusion of the terminal costs applied in the company base-case to these patients.

The ERG did not consider it plausible that non-infused patients would receive comparator costs and QALYs, and explored a scenario whereby the outcomes of these patients were modelled with an

alternative set of assumptions. The company provided Kaplan-Meier curves upon request for OS and EFS for patients not infused with tisagenlecleucel-T in the ELIANA and ENSIGN trials. The ERG noted that none of the ▆ patients who did not receive infusion were alive after 6 months, and considered it plausible that in practice these patients would be unlikely to receive other curative treatment after failure to receive tisagenlecleucel-T. The ERG also noted that none of this population achieved remission; therefore, it may be more appropriate to apply utility values associated with PD to this group.

The second scenario presented in Table 20 makes the following assumptions:

• These patients would not receive either of the comparator treatments, and would die according to the trial OS curves for this non-infused patients,

• All patients incur leukapheresis costs, with ▆▆ of those alive in the first month (half-cycle distribution) incurring bridging chemotherapy and ▆▆ receiving lymphodepleting chemotherapy costs as per the original model specifications.

• Bridging chemotherapy costs were used as a proxy for the chemotherapy regimen these patients would be likely to receive.

• Those who die at any point receive terminal care costs,

• All patients were assumed to be in the progressive disease health state while alive, and receive QALYs accordingly.

These scenarios make only small differences in the ICER, with additional terminal care costs adding £62 and £85 to the ICER for salvage chemotherapy and blinatumomab respectively. Separate modelling of non-infused patients reduced the total QALYs for tisagenlecleucel-T by ▆▆ in the pooled analysis, while also reducing costs by ▆▆▆, as a proportion of these patients no longer went on to receive the comparator therapies and SCT. This reduced the ICER versus blinatumomab by £285 compared to the ERG corrected base case.

Table 20 below explores the impact of inclusion of the terminal costs applied in the company base-case to these patients. These scenarios make only small differences in the ICER, with additional terminal care costs adding £62 and £85 to the ICER for salvage chemotherapy and blinatumomab respectively. Separate modelling of non-infused patients reduced the total QALYs for tisagenlecleucel-T by ▆▆ in the pooled analysis, while also reducing costs by ▆▆▆, as a

proportion of these patients no longer went on to receive the comparator therapies and SCT. This reduced the ICER versus blinatumomab by £285 compared to the ERG corrected base case.

Table 20 Modelling costs and QALYs for patients not infused with tisagenlecleucel-T (tisagenlecleucel-T PAS)

Comparator	Costs	QALYs	Incremental results			
			Costs	QALYs	ICER	Change in ICER
Company's base-case results (ERG corrected)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£28,806	-
Blinatumomab	■	■	■	■	£20,864	-
ERG Scenario: Terminal care costs applied to patients who died before infusion						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£28,868	£62
Blinatumomab	■	■	■	■	£20,949	£85
ERG Scenario: Non-infused patients independently modelled (ELIANA OS)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£28,801	-£6
Blinatumomab	■	■	■	■	£20,575	-£289
ERG Scenario: Non-infused patients independently modelled (ENSIGN OS)						
Tisagenlecleucel	■	■				
Salvage Chemotherapy	■	■	■	■	£28,818	£12
Blinatumomab	■	■	■	■	£20,584	-£280
ERG Scenario: Non-infused patients independently modelled (Pooled ELIANA & ENSIGN OS)						
Tisagenlecleucel	■	■				
Salvage chemotherapy	■	■	■	■	£28,807	£1
Blinatumomab	■	■	■	■	£20,579	-£285
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.3.2   Cure models applied to salvage chemotherapy OS data

As discussed in Section 5.2.6, the ERG considered consistency in the approach to curve fitting preferable between the treatment arms, and disagreed with the company's justification for the use of simple parametric extrapolation for salvage chemotherapy. Table 21 presents scenarios in which cure models are fitted to the OS data from Jeha *et al*. (2006), Hijiya *et al*. (2011), and Locatelli *et al*., (2009). In each scenario, EFS was based on OS (using the method described by the company in Section 5. 2.6. For each data source, the top three models are presented in terms of statistical fit, visual fit, and clinical plausibility; these curves are plotted for comparison in Figure 30.

The impact of these alternative scenarios is quite significant, with the ICERs ranging from £30,311 per QALY to £43,447 per QALY. In all scenarios the ICER increased relative to the company's base-case assumptions. Note that small changes in the ICER relative to blinatumomab were also observed when changing the OS data for salvage therapy. This is because patients who do not receive an infusion with tisagenlecleucel-T due to either AE's or manufacturing failure were assumed to receive the comparator therapies. Changes made to comparator therapy assumptions therefore also impact on costs and QALYs accrued in the tisagenlecleucel-T arm of the model.

Figure 30 Top three fitting mixture-cure models for salvage chemotherapy studies Jeha (A), Hijaya (B), Locatelli (C))
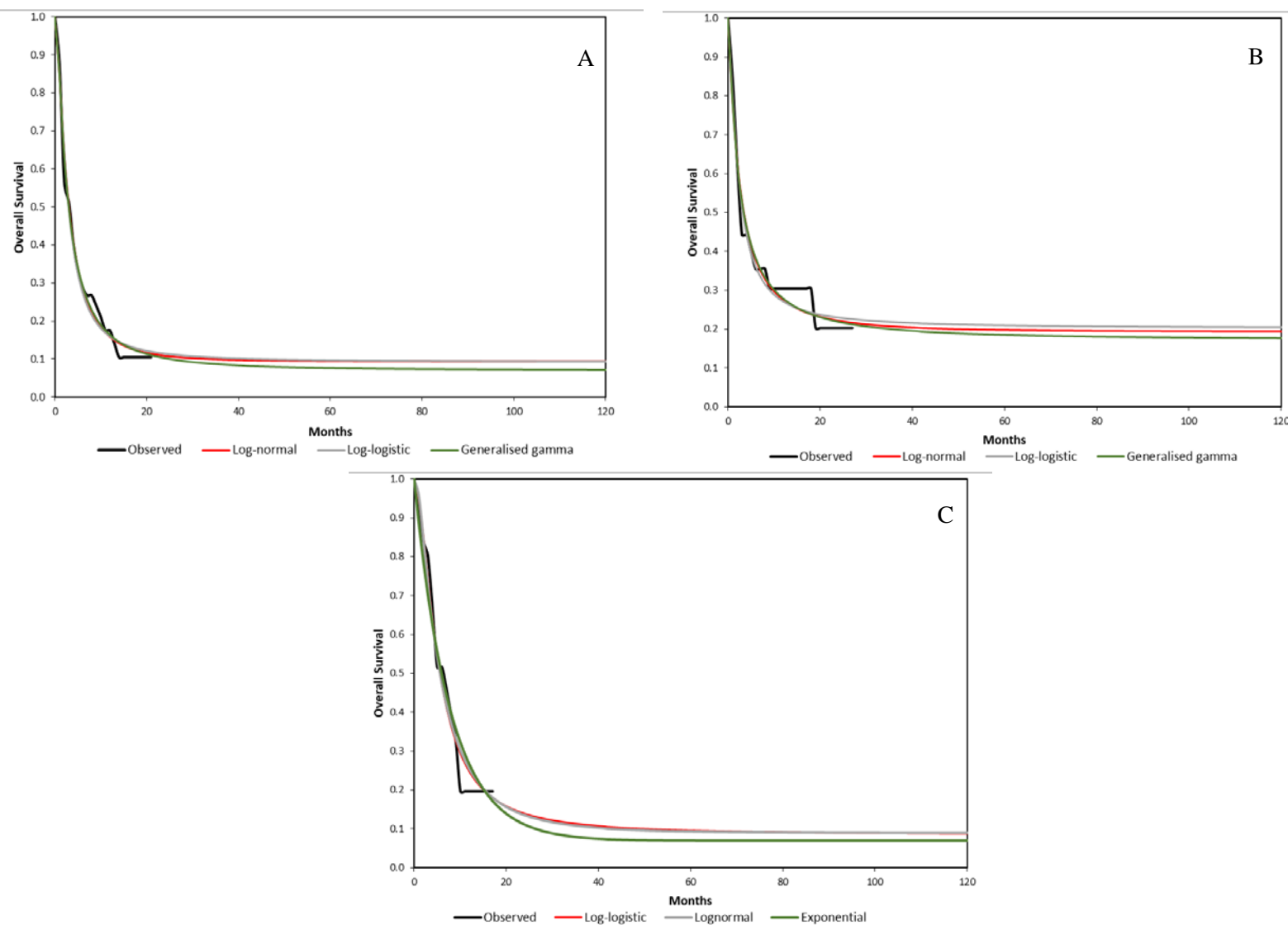
Table 21 Cure modelling approach for salvage chemotherapy (tisagenlecleucel-T PAS price)

Comparator			Incremental results			Change in ICER
	Costs	QALYs	Costs	QALYs	ICER	
Company's base-case results (ERG corrected)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£28,806	-
Blinatumomab	▮	▮	▮	▮	£20,864	-
ERG Scenario: Cure model applied for salvage chemotherapy (Jeha 2006, OS gen gamma)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£32,147	£3,341
Blinatumomab	▮	▮	▮	▮	£20,695	-£169
ERG Scenario: Cure model applied for salvage chemotherapy (Jeha 2006, OS lognormal)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£33,900	£5,094
Blinatumomab	▮	▮	▮	▮	£20,621	-£243
ERG Scenario: Cure model applied for salvage chemotherapy (Jeha 2006, OS loglogistic)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£33,868	£5,062
Blinatumomab	▮	▮	▮	▮	£20,622	-£242
ERG Scenario: Cure model applied for salvage chemotherapy (Hijiya 2011, OS gen gamma)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£39,183	£10,377
Blinatumomab	▮	▮	▮	▮	£20,572	-£292
ERG Scenario: Cure model applied for salvage chemotherapy (Hijiya 2011, OS lognormal)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£41,479	£12,672
Blinatumomab	▮	▮	▮	▮	£20,517	-£347
ERG Scenario: Cure model applied for salvage chemotherapy (Hijiya 2011, OS loglogistic)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£43,447	£14,641
Blinatumomab	▮	▮	▮	▮	£20,474	-£390
ERG Scenario: Cure model applied for salvage chemotherapy (Locatelli 2009, OS exponential)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£30,311	£1,505
Blinatumomab	▮	▮	▮	▮	£20,826	-£38
ERG Scenario: Cure model applied for salvage chemotherapy (Locatelli 2009, OS lognormal)						
Tisagenlecleucel	▮	▮				
Salvage Chemotherapy	▮	▮	▮	▮	£32,134	£3,328
Blinatumomab	▮	▮	▮	▮	£20,744	-£120
ERG Scenario: Cure model applied for salvage chemotherapy (Locatelli 2009, OS loglogistic)						

Comparator			Incremental results			Change in ICER
	Costs	QALYs	Costs	QALYs	ICER	
Tisagenlecleucel	▇▇▇	▇▇				
Salvage Chemotherapy	▇▇▇	▇▇	▇▇▇	▇▇	£32,063	£3,257
Blinatumomab	▇▇▇	▇▇	▇▇▇	▇▇	£20,747	-£117
Key: ICER, incremental cost-effectiveness ratio; MCM, mixture-cure model; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.3.3 Kuhlen *et al.* data for salvage chemotherapy

The ERG identified an alternative source of evidence on the prognosis of patients on salvage therapy, Kuhlen *et al.* (2017) [12], which was felt to be at least as plausible as the trials identified by the company to represent survival of patients receiving salvage therapy. As discussed in Section 5.2.6, there are some limitations associated with the use of this dataset in the present decision problem; however, the majority of these limitations were expected to result in bias that would favour tisagenlecleucel-T, thus potentially providing conservative cost-effectiveness outcomes.

The ERG digitised Kaplan-Meier curves for OS and EFS presented in Kuhlen (2017), and used the algorithm described by Guyot *et al*. (2012) [85] to generate pseudo-IPD, to which mixture cure models predicting long-term survival were fitted (see Figure 31). The cure fractions for OS ranged from 13.7% to 16.6% (Table 22): these are higher than those predicted by Jeha (2006) (the study used by the company in their base-case analysis), but lower than those predicted by Hijiya (2011). The lognormal model was considered the most plausible for EFS, and was applied in each of the ERG's scenarios.

Table 22 Cure fractions for overall survival and event-free survival, based on Kuhlen (2017)

Survival model	Overall survival	Event-free survival
Weibull	16.6%	11.2%
Lognormal	13.7%	4.3%
Generalised gamma	14.9%	10.1%

Figure 31 Top three fitting mixture-cure models for Kuhlen *et al.* OS data
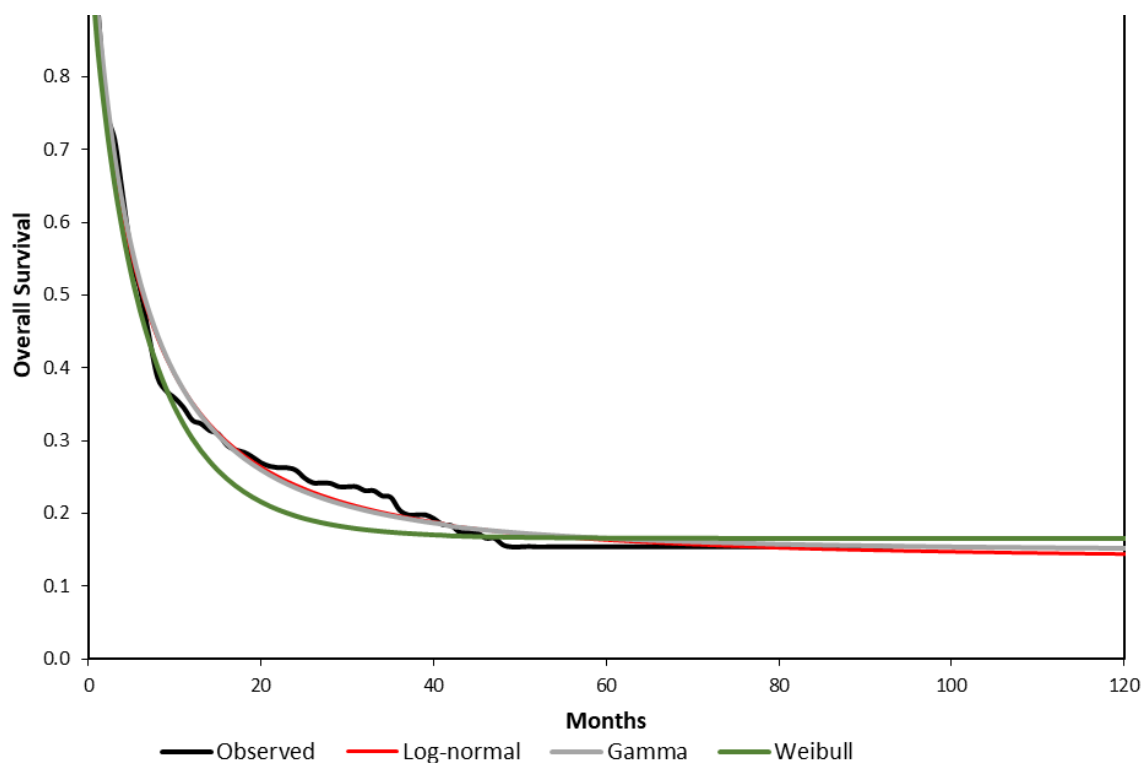
In this scenario, adverse event rates for salvage therapy were based on those reported by Kantarjian *et al.* (2017), and rates of SCT were extracted from Kuhlen *et al.* (2017), where 61 of 173 (35%) patients who received salvage therapy in the trial received subsequent SCT.

The modelling of survival of salvage therapy patients based on data from Kuhlen (2017) resulted in additional costs and QALYs in this arm. The majority of the incremental cost increase seen in these scenarios relative to base-case and scenarios presented in Section 5.2.10 is due to a greater proportion of these patients receiving SCT. As a result, the ICER for tisagenlecleucel-T versus salvage chemotherapy increased from £28,806 in the company (corrected) base-case, to between £37,564 and £39,181, dependent on choice of survival model.

Table 23 Survival associated with salvage chemotherapy using Kuhlen *et al*. (tisagenlecleucel-T PAS price)

| Comparator | Costs | QALYs | Incremental results | | ICER | Change in ICER |
			Costs	QALYs		
Company's base-case results (ERG corrected)						
Tisagenlecleucel	▉	▉				
Salvage Chemotherapy	▉	▉	▉	▉	£28,806	-
Blinatumomab	▉	▉	▉	▉	£20,864	-
ERG Scenario: Cure model applied for salvage chemotherapy (OS lognormal, EFS lognormal (MCM))						
Tisagenlecleucel	▉	▉				
Salvage Chemotherapy	▉	▉	▉	▉	£37,564	£8,758
Blinatumomab	▉	▉	▉	▉	£20,584	-£279
ERG Scenario: Cure model applied for salvage chemotherapy (OS Weibull, EFS lognormal (MCM))						
Tisagenlecleucel	▉	▉				
Salvage Chemotherapy	▉	▉	▉	▉	£39,181	£10,375
Blinatumomab	▉	▉	▉	▉	£20,539	-£325
ERG Scenario: Cure model applied for salvage chemotherapy (OS gamma, EFS lognormal (MCM))						
Tisagenlecleucel	▉	▉				
Salvage Chemotherapy	▉	▉	▉	▉	£38,432	£9,626
Blinatumomab	▉	▉	▉	▉	£20,560	-£304
Key: ICER, incremental cost-effectiveness ratio; MCM, mixture-cure model; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.3.4 Prevalence and duration of IVIG use

As discussed in Section 5.2.9, company's base-case assumed all patients with B-cell aplasia (73.33%) would require treatment with intravenous immunoglobulin (IVIG) for the duration of their aplasia. The ERG considered this overly conservative and clinical advice received by the ERG suggested that only those patients who had frequent infections and low immunoglobulin levels would require immunoglobulin replacement, with prophylaxis and antibiotic treatment the preferred management strategy for most patients. Therefore, the ERG present a scenario in which only ▉▉▉▉ of patients would receive IVIG for the period of 11.4 months included in the company's base-case analysis. This is in line with the proportion of patients with hypogammaglobulinaemia in the ELIANA trial.

The 11.4 month duration of IVIG treatment used by the company was derived from a median duration of B-cell aplasia reported in the ELIANA trial. The use of median duration may be inappropriate for calculating the long-term costs of IVIG use, given that around 70% of patients had not reached B-cell

recovery by the latest ELIANA cut-off of 24 months. It is therefore likely that many patients will suffer prolonged aplasia, which could persist for the duration of remission.

As noted in Section 5.2.9 the ERG has concerns that the company base case significantly underestimates the average duration of IVIG treatment, due to the use of a median B-cell aplasia duration. In order to explore the potential impact of lifelong immunoglobulin deficiency in some patients, the final scenario presented in Table 24 assumes all patients in the EFS health state have B-cell aplasia, and that ▇ of this group have hypogammaglobulinaemia requiring IVIG treatment. This results of these analyses all result in an increase in the ICER of tisagenlecleucel-T relative to both salvage chemotherapy (range £27,619 to £35,103) and blinatumomab (range £19,232 to £29,517) respectively.

Table 24 Alternative IVIG use prevalence and duration (tisagenlecleucel-T PAS price)

Comparator			Incremental results			Change in ICER
	Costs	QALYs	Costs	QALYs	ICER	
Company's base-case results (ERG corrected)						
Tisagenlecleucel	▇	▇				
Salvage Chemotherapy	▇	▇	▇	▇	£28,806	-
Blinatumomab	▇	▇	▇	▇	£20,864	-
IVIG used only in patients with hypogammaglobulinaemia						
Tisagenlecleucel	▇	▇				
Salvage Chemotherapy	▇	▇	▇	▇	£27,619	-£1,188
Blinatumomab	▇	▇	▇	▇	£19,232	-£1,632
ERG Scenario: 3-year IVIG duration (hypogammaglobulinaemia only)						
Tisagenlecleucel	▇	▇				
Salvage Chemotherapy	▇	▇	▇	▇	£29,321	£515
Blinatumomab	▇	▇	▇	▇	£21,572	£708
ERG Scenario: 5-year IVIG duration (hypogammaglobulinaemia only)						
Tisagenlecleucel	▇	▇				
Salvage Chemotherapy	▇	▇	▇	▇	£30,457	£1,651
Blinatumomab	▇	▇	▇	▇	£23,132	£2,269
ERG Scenario: IVIG duration based on EFS (HGG)						
Tisagenlecleucel	▇	▇				
Salvage Chemotherapy	▇	▇	▇	▇	£35,103	£6,296
Blinatumomab	▇	▇	▇	▇	£29,517	£8,654
Key: HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.3.5 Stem-cell transplant prevalence and utility

As discussed in Section 5.2.8.3, the ERG considers the utility decrement of -0.57 applied to recipients of HSCT to persist for too long, given the gradual recovery and reduction in AE frequency over time. The ERG performed a scenario analysis in which patients received a decrement of -0.57 for 3 months following SCT, which reduces to -0.13 for 9 months, to reflect the improvement in symptoms over time seen in Felder-Puig *et al.* [61]. The results in Table 25 show this analysis has only a marginal impact upon the cost effectiveness of tisagenlecleucel-T, apportioning equal QALY gains to each treatment arm according to the proportion of patients receiving SCT.

Two further scenario analyses are presented in Table 25 which recognise differences between the use of SCT in the tisagenlecleucel-T trials to consolidate remission in some trials, and the anticipated intention to use tisagenlecleucel-T as a curative therapy in the NHS. The ERG considered the ▮▮▮ of patients modelled to receive allogeneic HSCT in the tisagenlecleucel-T arm to be an overestimation, and it may be the case that in practice, no patients who achieve remission on this treatment will receive SCT. This assumption reduces the ERG corrected base-case ICER by £2,377 versus salvage chemotherapy, and £3,139 versus blinatumomab.

The final scenario presented in Table 25 explores the impact upon the ICER if all patients in EFS (▮▮▮ in the company base-case) at month 1 incur the cost of SCT, in a scenario where tisagenlecleucel-T is used only to induce remission, but assumes the same impact upon overall survival. While this increases the ICER by £12,774 and £17,304, this is a highly conservative assumption.

Table 25 Alternative assumptions for stem cell transplant uptake and QoL (tisagenlecleucel-T PAS price)

| | | | Incremental results | | | |
Comparator	Costs	QALYs	Costs	QALYs	ICER	Change in ICER
Company's base-case results (ERG corrected)						
Tisagenlecleucel	▮▮▮	▮▮▮				
Salvage Chemotherapy	▮▮▮	▮▮▮	▮▮▮	▮▮▮	£28,806	-
Blinatumomab	▮▮▮	▮▮▮	▮▮▮	▮▮▮	£20,864	-
ERG Scenario: Lower disutility applied from 3 – 12 months post-SCT						
Tisagenlecleucel	▮▮▮	▮▮▮				
Salvage Chemotherapy	▮▮▮	▮▮▮	▮▮▮	▮▮▮	£28,804	-£2
Blinatumomab	▮▮▮	▮▮▮	▮▮▮	▮▮▮	£21,095	£231
ERG Scenario: 0% of tisagenlecleucel-T patients receive SCT costs and disutility						
Tisagenlecleucel	▮▮▮	▮▮▮				
Salvage Chemotherapy	▮▮▮	▮▮▮	▮▮▮	▮▮▮	£26,429	-£2,377

Blinatumomab	██████	███	███████	██	£17,725	-£3,139
ERG Scenario: 100% of tisagenlecleucel-T patients receive SCT costs and disutility						
Tisagenlecleucel	██████	███				
Salvage Chemotherapy	█████	███	███████	██	£40,412	£11,606
Blinatumomab	██████	███	███████	██	£36,554	£15,690
Key: ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; PAS, patient access scheme; QALYs, quality-adjusted life year; SCT, stem cell transplant						

6.3.6   Duration of treatment with blinatumomab

The ERG explored a scenario where the duration of treatment of blinatumomab was limited to two cycles. The proportion of patients receiving one and two cycles was 96% and 31% respectively, as per the company base-case analysis. This was based on advice from the clinical advisor to the ERG, who noted that patients would be unlikely to receive more than two courses in practice before progressing to SCT.

Table 26 presents the results of this scenario. The impact of limiting the number of treatment cycles was a cost saving in the tisagenlecleucel-T arm and the blinatumomab arm of ████ and ████████ respectively. The results of this scenario should be interpreted with caution given the efficacy of blinatumomab was not altered to reflect patients receiving only two cycles of treatments rather than the five cycles received in von Stackelberg et al. (2016)'.

Table 26 Alternative assumption for blinatumomab treatment duration (tisagenlecleucel-T PAS price)

Comparator			Incremental results			Change in ICER
	Costs	QALYs	Costs	QALYs	ICER	
Company's base-case results (ERG corrected)						
Tisagenlecleucel	█████	███				
Salvage Chemotherapy	█████	███	███████	██	£28,806	-
Blinatumomab	██████	███	███████	██	£20,864	-
ERG Scenario: Patients only receive up to two cycles of blinatumomab						
Tisagenlecleucel	█████	███				
Salvage Chemotherapy	█████	███	███████	██	£28,721	-£85
Blinatumomab	██████	███	███████	██	£22,913	£2,050
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life year;						

6.3.7   Usage of ICU beds for patients with cytokine release syndrome

The ERG had concerns that the provision of tisagenlecleucel-T in specialist centres may require that ICU beds are held free in these centres during the period a patient is considered to be at risk of CRS to ensure availability. This potentially represents an additional cost associated with treatment with tisagenlecleucel-T.

The ERG explored the incorporation of the cost of holding ICU beds during the CRS risk period. The holding period was assumed to be the mean time to CRS, based on data extracted from ELIANA, ENSIGN and B2101J trials, and was estimated as ████████. The cost was applied to all patients receiving tisagenlecleucel-T (i.e. not just those experiencing CRS).

In this scenario, the addition of this resource in the analysis resulted in an increase of costs in the tisagenlecleucel-T arm of £8,153, leading to a modest increases in the ICER by £1,110 and £1,526 for salvage chemotherapy and blinatumomab respectively.

Table 27 Inclusion of cost of holding ICU beds during CRS risk period (tisagenlecleucel-T PAS price)

Comparator			Incremental results			Change in ICER
	Costs	QALYs	Costs	QALYs	ICER	
Company's base-case results (ERG corrected)						
Tisagenlecleucel	████	██				
Salvage Chemotherapy	████	██	████	██	£28,806	-
Blinatumomab	████	██	████	██	£20,864	-
ERG Scenario: Inclusion of cost of holding ICU beds during CRS risk period						
Tisagenlecleucel	████	██				
Salvage Chemotherapy	████	██	████	██	£29,916	£1,110
Blinatumomab	████	██	████	██	£22,390	£1,526
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life year; CRD, cytokine release syndrome						

6.3.8 Health-related quality of life for tisagenlecleucel-T patients

As outlined in Section 5.2.6.2, the ERG considered the uncertainty around the short-term treatment and adverse event-related utility decrements for tisagenlecleucel-T applied by the company might be better accounted for using utility values elicited from ELIANA trial participants. Table 28 presents the results of a scenario in which patients in the progressive disease health state have a utility of ███, with a score of ███ for those in event-free survival, and 0.91 for those in 'long-term survival', as derived from those who survived >5 years in Kelly *et al* (2015) [56]. As the trial-derived utility values

already account for disutilities associated with treatment and AEs, the externally sourced values have been removed from the model in this scenario.

The two scenarios below represent different assumptions regarding the beginning of 'long-term survival'. The ELIANA HRQoL data was elicited over two years, therefore the use of this time-point assumes patients would return to the higher utility score derived from the Kelly study, this assumes a recovery in patients' general HRQoL, and improvements associated with decreasing AE frequency over time. The post-5-year application of LTS utilities assumes patients do not return to full health until they are considered 'cured', and represents a more conservative scenario, albeit in line with the population from which the data is derived (Kelly *et al*.).

Table 28 Scenarios including alternate health state utility values (tisagenlecleucel-T PAS price)

| Comparator | Costs | QALYs | Incremental results | | | Change in ICER |
			Costs	QALYs	ICER	
Company's base-case results (ERG corrected)						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£28,806	-
Blinatumomab	███	██	███	██	£20,864	-
ERG Scenario: Tisagenlecleucel-T ELIANA EFS & PD utilities, LTS from Kelly *et al*. (>2 years)						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£29,327	£521
Blinatumomab	███	██	███	██	£21,386	£522
ERG Scenario: Tisagenlecleucel-T ELIANA EFS & PD utilities, LTS from Kelly *et al*. (>5 years)						
Tisagenlecleucel	███	██				
Salvage chemotherapy	███	██	███	██	£29,764	£958
Blinatumomab	███	██	███	██	£21,829	£966
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.4 ERG alternative base-case

Table 29 Results of corrections and scenarios included in ERG base case (tisagenlecleucel-T PAS price)Table 29 presents the results of the ERG alternative base-case analysis. These incorporate a number of changes to key model parameters and assumptions, which were previously explored individually in Section 6.3.

The ERG alternative base-case analysis includes the following changes to the company base-case analysis:

- ERG mortality correction,
- Addition of new salvage chemotherapy data, use of mixture cure model for salvage chemotherapy OS and EFS,
- ERG's preferred OS extrapolations for tisagenlecleucel-T and blinatumomab,
- Application of ELIANA utility values for tisagenlecleucel-T patients in EFS and PD for up to two years, Kelly *et al.* long-term survival utility post two years,
- Application of a lower disutility for patients between 3 and 12 months post-SCT,
- Models costs and QALYs for patients who did not go on to receive infusion with tisagenlecleucel-T separately, based on ELIANA & ENSIGN OS data,
- IVIG is only used in those patients with hypogammaglobulinaemia,
- Assumes patients will only receive 2 cycles of blinatumomab,
- Incorporates the cost of holding ICU beds during CRS risk period.

The ERG considers this analysis to represent a more plausible estimate of the cost-effectiveness of tisagenlecleucel-T, and to better reflect the uncertainties around the data and assumptions in the company's base-case discussed throughout Section 5 of this report. The impact of three other outstanding areas of uncertainty was explored in scenarios presented in Table 30. The ERG notes that salvage chemotherapy is unlikely to yield larger QALY gains than blinatumomab as seen in the ERG preferred base-case. It is not unrealistic to expect roughly similar efficacy given the evidence previously discussed, and the observed differences are likely due to the substantial uncertainty in the respective estimates of effectiveness, and the poorer than expected outcomes of paediatric blinatumomab patients in von Stackelberg *et al.*, rather than a true difference in effects.

Under the ERG's alternative set of assumptions, based on a probabilistic analysis, the ICER is £48,265 per QALY for tisagenlecleucel-T compared with salvage therapy, and £29,501 per QALY for tisagenlecleucel-T compared with blinatumomab.

Table 29 Results of corrections and scenarios included in ERG base case (tisagenlecleucel-T PAS price)

Comparator			Incremental results			ΔICER from CBC
	Costs	QALYs	Costs	QALYs	ICER	
Company's base-case results						
Tisagenlecleucel	▮▮▮	▮▮				
Salvage Chemotherapy	▮▮▮	▮▮	▮▮▮	▮▮	£25,404	-

Comparator	Costs	QALYs	Incremental results			ΔICER from CBC
			Costs	QALYs	ICER	
Blinatumomab	███	███	███	███	£18,392	-
1. Company's base-case results including ERG's mortality calculation correction						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£28,806	£3,402
Blinatumomab	███	███	███	███	£20,864	£2,471
2. Salvage chemotherapy OS and EFS data from Kuhlen *et al*. 2017. Mixture cure model (OS lognormal, EFS lognormal)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£33,110	£7,706
Blinatumomab	███	███	███	███	£18,147	-£245
3. Blinatumomab OS log-logistic mixture cure model (EFS based on OS)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,368	-£36
Blinatumomab	███	███	███	███	£19,051	£659
4. Tisagenlecleucel-T OS log-logistic mixture cure model (EFS gen. gamma)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£28,203	£2,798
Blinatumomab	███	███	███	███	£21,284	£2,891
5. Tisagenlecleucel-T ELIANA EFS & PD utilities, LTS from Kelly *et al*. (>2 years)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,808	£404
Blinatumomab	███	███	███	███	£18,796	£404
6. Lower disutility applied from 3 – 12 months post-SCT						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,403	-£1
Blinatumomab	███	███	███	███	£18,572	£179
7. Non-infused patients independently modelled (Pooled ELIANA & ENSIGN OS)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,371	-£33

Comparator	Costs	QALYs	Incremental results			ΔICER from CBC
			Costs	QALYs	ICER	
Blinatumomab	███	███	███	███	£18,108	-£285
8. IVIG used only in patients with hypogammaglobulinaemia (11.4 month duration)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£24,359	-£1,046
Blinatumomab	███	███	███	███	£16,956	-£1,436
9. Patients receive only 2 cycles of blinatumomab						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£25,330	-£75
Blinatumomab	███	███	███	███	£20,196	£1,803
10. Cost of holding ICU beds during CRS risk period included						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£26,382	£978
Blinatumomab	███	███	███	███	£19,735	£1,342
ERG deterministic base-case (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£45,397	£19,992
Blinatumomab	███	███	███	███	£27,732	£9,339
ERG probabilistic base-case (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)						
Tisagenlecleucel	███	███				
Salvage Chemotherapy	███	███	███	███	£48,265	£22,861
Blinatumomab	███	███	███	███	£29,501	£11,109
Key: CBC, company's base-case; HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; MCM, mixture-cure model; PAS, patient access scheme; QALYs, quality-adjusted life year						

6.5 Exploratory analyses on ERG alternative base-case

There are significant unresolved uncertainties around the use of SCT duration of IVIG use and extrapolation of OS for tisagenlecleucel-T, which may not be resolved without clinical experience of tisagenlecleucel-T in an NHS setting. Table 30 presents other iterations of ERG's deterministic base case in which the following assumptions are explored in addition to scenarios 1 to 10 in Table 29.

- 0% of patients on tisagenlecleucel-T receive SCT. Tisagenlecleucel-T is demonstrated to be truly 'curative' in and of itself, therefore SCT will never be used to consolidate remission,
- 100% of patients in EFS (half-cycle distribution, ERG base-case 92.75%) on tisagenlecleucel-T receive a stem-cell transplant and achieve the same outcomes (assuming tisagenlecleucel-T is bridge to SCT),
- B-cell aplasia and HGG persist for an average of 3 years,
- B-cell aplasia and HGG persist in some patients indefinitely. IVIG use continues in all patients with HGG indefinitely (mean duration of treatment 6.5 years).

Assuming no patients are to receive SCT as consolidation for remission induced by tisagenlecleucel-T, the ICER decreases by £4,122 versus salvage chemotherapy, and £3,831 versus blinatumomab from the ERG's preferred base-case; the ERG considers this a plausible scenario in NHS practice. If all patients who achieve EFS are to receive SCT, the ICER would increase by £19,833 versus salvage chemotherapy, and £18,401 versus blinatumomab. This scenario assumes a significant change from the intended use of tisagenlecleucel-T, but is in line with the use of other CAR-T cell therapies as a bridge to SCT.

The two further scenarios explore the uncertainty associated with long-term B-cell aplasia, which has been observed in the majority of patients in the three tisagenlecleucel-T trials. While these scenarios are more optimistic than the company's base-case terms of the proportion of patients requiring IVIG, it assumes patients who have immunoglobulin deficiency will require replacement either for an extended period, or indefinitely, reflecting the KM curve presented in Figure 26. If patients with immunoglobulin deficiency require IVIG replacement for 3 years, the ERG's base case ICER increases by £3,079 versus salvage chemotherapy, and by £2,963 versus blinatumomab. If HGG persists in some patients for as long as they remain in remission and requires IVIG, the ICER increases by £12,945 versus salvage chemotherapy, and £12,460 versus blinatumomab.

A final scenario explores the uncertainty around the long-term effectiveness of tisagenlecleucel-T in which one of the most pessimistic interpretations of the long-term survival of tisagenlecleucel-T assumed. This is a worst-case scenario in which the medium term benefits observed in the available trial data fail to persist over a longer-term. In this is analysis a mixture cure model using lognormal function is applied to the tisagenlecleucel-T OS data. This predicts a cure-fraction ▮▮▮▮ compared ▮▮▮▮ in the company's base and ▮▮▮▮ in the ERG's base-case. In this scenario, the number of QALYs gained by tisagenlecleucel-T decreases substantially, resulting in an increase in the ICERS to £74,322 and £44,299 for salvage chemotherapy and blinatumomab respectively.

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Table 30 Alternate ERG base-case assumptions (tisagenlecleucel-T PAS price)

Comparator	Costs	QALYs	Incremental results Costs	QALYs	ICER	ΔICER from ERG BC
ERG deterministic base-case						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£45,397	-
Blinatumomab	███	██	███	██	£27,732	-
ERG base-case: 0% of tisagenlecleucel-T patients receive SCT						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£41,274	-£4,122
Blinatumomab	███	██	███	██	£23,900	-£3,831
ERG base-case: 100% of patients in EFS receive SCT						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£65,229	£19,833
Blinatumomab	███	██	███	██	£46,133	£18,401
ERG base-case: 3-year duration of IVIG use in patients with HGG						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£48,475	£3,079
Blinatumomab	███	██	███	██	£30,695	£2,963
ERG base-case: IVIG use based on ongoing HGG in patients in EFS						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£58,342	£12,945
Blinatumomab	███	██	███	██	£40,192	£12,460
ERG base-case: tisagenlecleucel-T OS based on lognormal cure model						
Tisagenlecleucel	███	██				
Salvage Chemotherapy	███	██	███	██	£74,322	£28,925
Blinatumomab	███	██	███	██	£44,299	£16,567
Key: HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; PAS, patient access scheme; QALYs, quality-adjusted life year; SCT, stem cell transplant						

6.6   Conclusions from ERG analyses

The ERG has presented a number of additional analyses carried out in a number of stages. The first stage addressed a calculation error in the company's revised model. The impact of this change was to increase the ICER from £25,404 per QALY to £28,806 per QALY for tisagenlecleucel-T compared with salvage therapy, and from £18,392 per QALY to £20,864 per QALY for tisagenlecleucel-T compared with blinatumomab.

Using the corrected and updated model, the ERG then presented a number of analyses considering a range of issues raised in Section 5.2. These scenario analyses addressed the following issues:

- Alternative assumptions around the prognosis and treatment of non-infused patients in the tisagenlecleucel-T arm regarding their OS, and their associated costs and QALYs,
- Methods used to analyse extrapolate OS data,
- The source of clinical data used to estimate the survival of patients on salvage chemotherapy
- B-cell aplasia duration and costs of IVIG,
- Post-SCT quality of life and anticipated SCT uptake in practice,
- Number of lines of blinatumomab treatment modelled,
- The health state utilities used in the model.

The most of important these scenarios related to the use of alternative parametric functions to model long-term OS for tisagenlecleucel-T patients and the use of alternative source of clinical data for salvage chemotherapy. The ERG alternative base-case, based on a probabilistic analysis, estimated a tisagenlecleucel-T to be more costly (cost difference of ▮▮▮▮ and ▮▮▮▮) and more effective (QALY gain of ▮▮▮ and ▮▮▮) compared with salvage therapy and blinatumomab, and suggests that the ICER for tisagenlecleucel-T compared with salvage therapy is £48,265 per QALY and compared with blinatumomab is £29,501.

A further series of exploratory analyses were conducted on the ERG base-case to explore uncertainties regarding the uptake of SCT in patients receiving and the duration of IVIG use. Both of these issues were found to have significant impact on the estimated ICER and suggest that the most plausible (deterministic) ICER is likely to be between £41,274 per QALY and £65,229 per QALY.

7   End of life

The CS (Table 24, p87 CS) presents evidence to support tisagenlecleucel-T as an end-of-life therapy.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The median OS in patients with r/r B-cell ALL treated using standard care is reported to be less than 24 months. Median OS with blinatumomab reported in von Stackelberg *et al.* was 7.5 months (95% CI 4.0 to 11.8 months). Evidence from other trials of blinatumomab also suggests median survival less than 24 months. The TOWER trial reported a median OS of 9.9 months for blinatumomab in patients aged under 35 years of age and the RIALTO trial, an expanded access study of blinatumomab, reported a median OS of 9.8 months. Median survival data for FLA-IDA are not known as no clinical data was found in the relevant population.

The modelled (undiscounted) mean overall survival was ▆▆▆ years for salvage chemotherapy and ▆▆▆ years for blinatumomab in the company's base-case model. In the ERG base-case using Kuhlen *et al.* (2017) as a source of effectiveness data for salvage chemotherapy, and alternative extrapolation assumptions for blinatumomab, the mean (undiscounted) overall survival was ▆▆▆ years for salvage chemotherapy and ▆▆▆ years for blinatumomab.

Criterion 2: There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

The median OS for tisagenlecleucel-T was reported as 23.8 and ▆▆▆ months in the ENSIGN and B2101J studies, respectively. Median OS had not been reached at the latest ELIANA data cut. The pooled median OS was ▆▆▆ months (▆▆▆▆▆▆▆▆▆▆). In the company's base-case, the modelled (undiscounted) mean overall survival benefits of tisagenlecleucel were ▆▆▆ years compared with blinatumomab and ▆▆▆ years compared with salvage chemotherapy. In the ERG base-case using Kuhlen *et al.* (2017) as a source of effectiveness data for salvage chemotherapy and alternative extrapolation assumptions for tisagenlecleucel-T and blinatumomab, the mean (undiscounted) overall survival benefits were ▆▆▆ years compared with blinatumomab and ▆▆▆ years compared with salvage chemotherapy.

The ERG consider it uncertain whether the first criterion is met, as this depends entirely upon the use of a mean or median life expectancy. The ERG considers it probable, but uncertain, that the second criterion is met. This is because of the considerable uncertainty in assessing accurately the extension

of life with tisagenlecleucel-T due to significant differences between the tisagenlecleucel-T studies and the comparator studies (von Stackelberg *et al*., Jeha *et al*., and Kuhlen *et al*.).

8 Overall conclusions

Clinical effectiveness

The results presented in the CS of the ELIANA, ENSIGN and B2101J trials demonstrate a beneficial effect of tisagenlecleucel-T, with a pooled median OS of ▮▮▮▮▮▮. Comparisons with trials of blinatumomab and clofarabine suggested a strong benefit of tisagenlecleucel-T with hazard ratios of ▮▮▮ when compared to blinatumomab and ▮▮▮ with clofarabine.

The ERG has several concerns with the analyses presented. There is a delay between enrolment and infusion with tisagenlecleucel-T. The evidence submitted in the original CS presented survival curves only from time of infusion, not time of enrolment, thereby excluding any events occurring between these times. The ERG considers that this does not represent results for a true intention-to-treat population, and so overstates the benefits of tisagenlecleucel-T. The company, on request, supplied survival curves that included all patients enrolled. These showed markedly lower survival rates. Based on ELIANA the ERG considers that around 45% of patients will be event free at 12 months, and around 42% at 24 months; around 68% of patients will be alive at 12 months and 58% at 24 months.

The median time between enrolment and infusion of tisagenlecleucel-T in all three trials was substantially longer than the 3 to 4 weeks estimated in the CS. This has considerable implication for eligible patients due to the pace of disease progression and their short-estimated life expectancy.

No head-to-head comparison of tisagenlecleucel-T with any other treatment was presented. All comparisons were based on adjusted or unadjusted indirect comparisons, which are prone to bias if adjustment is not perfect. The comparisons were placed at further risk of bias because, as noted above, data on tisagenlecleucel-T was measured from time of infusion, excluding patients who were not infused. The ERG considers this to be an unfair comparison with patients in other trials, who were never considered for infusion, and therefore considers the results of the comparative MAIC analysis to be unreliable.

The ERG has substantial concerns regarding the comparability of Stackelberg *et al*. and Jeha *et al*. trials to the tisagenlecleucel-T trials, with several differences in study design and baseline characteristics. The ERG is unclear why only these trials were used as comparators, given that the company and the ERG identified other relevant trials. The ERG also noted that no evidence was presented to justify using clofarabine as a proxy for FLA-IDA. The ERG does not consider Stackelberg *et al*. or Jeha *et al*. as suitable evidence of the comparators and notes the availability of alternative sources of comparator effectiveness data.

In conclusion, the ERG considers that there is significant uncertainty regarding the effect size and provision of tisagenlecleucel-T in the UK. While there is evidence that tisagenlecleucel-T is likely to be beneficial and extend life, the size of this benefit, and how it compares to alternative therapies, is highly uncertain.

Cost effectiveness

The company's base-case deterministic ICERs for tisagenlecleucel-T compared to blinatumomab was £25,404 per QALY and £18,392 per QALY compared to salvage chemotherapy (PAS price). The key drivers of cost effectiveness were the extrapolation of tisagenlecleucel-T OS data and the source of evidence for the comparator regimens.

The ERG's critique primarily focuses on key uncertainties identified clinical inputs used in the model, which primarily stem from the lack of head to evidence and immaturity of the clinical data for tisagenlecleucel-T. The ERG's exploratory analysis focused on exploring a number of these uncertainties and a new base-case was proposed, in which alternative assumptions regarding the extrapolation of the OS data for tisagenlecleucel-T were considered and an alternative source of clinical data was used to model salvage chemotherapy. The ERG alternative base-case analysis estimated the ICER for tisagenlecleucel-T compared to blinatumomab to be £29,501 per QALY per QALY and £48,265 per QALY per QALY compared to salvage chemotherapy (PAS price).

Further exploratory analysis on the ERG's base-case also explored remaining uncertainties regarding the persistence of B-cell aplasia, a common AE associated with tisagenlecleucel-T, and the uptake of SCT in patients receiving tisagenlecleucel-T. The ICERs based on this exploratory analysis ranged from between £23,900 per QALY and £46,133 per QALY compared with blinatumomab and between £41,274 per QALY and £65,229 per QALY compared with salvage chemotherapy.

Despite the ERG's attempt to address the key uncertainties, data limitations imply that key uncertainties remain which cannot be fully explored. Firstly, the immaturity of the available OS data and long period over which gains were extrapolated imply significant uncertainty regarding the long-term outcomes of patients receiving tisagenlecleucel-T, which will not be fully resolved until further date collection is undertaken. Secondly, the cost-effectiveness estimates are based on an uncontrolled comparison and, while the ERG explored an alternative source of comparator data (Kuhlen *et al* [12]), these results will be affected by unquantifiable bias. Finally, the implementation of services to deliver CAR T-cell therapies within the UK context raises wider issues with implications in terms of potential

additional resource use/costs to the NHS (e.g. costs of staff training and/or infrastructure, timing for credit for non-infused product, etc.), which cannot be fully quantified within the scope of this review.

8.2 Implications for research

Further head-to-head RCT evidence and longer follow-up in r/r B-cell ALL patients, treated with tisagenlecleucel-T, is required

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10 Appendices

10.1 Baseline characteristics of the full ITT population

Table 31 Patient baseline characteristics for the full ITT population in ELIANA, ENSIGN and B2101J

Characteristic	ELIANA (N=▮)	ENSIGN (N=73)	B2101J (N=▮)[a]
Demographics			
Age (years)			
Mean (SD)	▮	▮	▮
Median	▮	▮	▮
Min–Max	▮	▮	▮
Sex, n (%)			
Female	▮	▮	▮
Male	▮	▮	▮
Race, n (%)			
White	▮	▮	▮
Black	▮	▮	▮
Asian	▮	▮	▮
Pacific Islander	▮	▮	▮
Other	▮	▮	▮
Ethnicity, n (%)			
Hispanic or Latino	▮	▮	▮
Mixed Ethnicity	▮	▮	▮
Other	▮	▮	
Weight for tisagenlecleucel-T manufacturing (kg)[b]			
n	▮	▮	▮
Mean (SD)	▮	▮	▮
Median	▮	▮	▮
Min-Max	▮	▮	▮
Karnofsky/Lanksy performance status, n (%)			
100	▮	▮	▮
90	▮	▮	▮
80	▮	▮	▮
70	▮	▮	▮
60	▮	▮	▮
50	▮	▮	▮
<50	▮	▮	▮
Missing	▮	▮	▮
Disease history and prior therapies			
Diagnosis of disease, n (%)			

B-cell ALL	�▬	▬	▬
T-cell ALL	▬	▬	▬
Age at initial diagnosis (years)			
Mean (SD)	▬	▬	▬
Median	▬	▬	▬
Min-Max	▬	▬	▬
Prior haematopoietic stem cell transplant (SCT)			
0	▬	▬	▬
1	▬	▬	▬
2	▬	▬	
Disease status, n (%)			
Primary refractory	▬	▬	▬
Chemo-refractory	▬	▬	▬
Relapsed disease			
Number of previous lines of therapy, n (%)			
Mean (SD)	▬	▬	▬
Median	▬	▬	▬
Min-Max	▬	▬	▬
Time since initial diagnosis to first relapse (months)[b, c]			
n	▬	▬	▬
Mean (SD)	▬	▬	▬
Median	▬	▬	▬
Min-Max	▬	▬	▬
Time since initial diagnosis to first relapse category (months), n (%)[c]			
<18	▬	▬	▬
18 to 36	▬	▬	▬
>36	▬	▬	▬
N/A	▬	▬	▬
Time since most recent relapse to tisagenlecleucel-T infusion (months)[b, c]			
n	▬	▬	▬
Mean (SD)	▬	▬	▬
Median	▬	▬	▬
Min-Max	▬	▬	▬

10.2 Time to B-cell recovery

Figure 32 Kaplan-Meier curve for time to B-cell recovery in peripheral blood in patients who achieved CR or CRi in ELIANA

Figure 33 Kaplan-Meier curve for time to B-cell recovery in peripheral blood in patients who achieved CR or CRi in ENSIGN
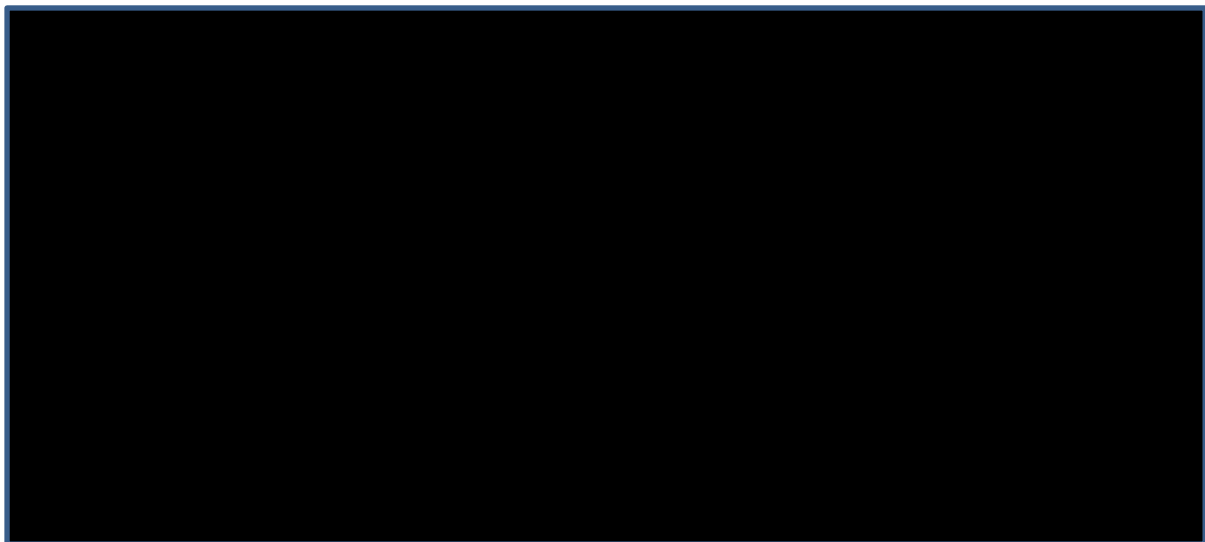
10.3 Kaplan-Meier curves for OS all clofarabine combination trials
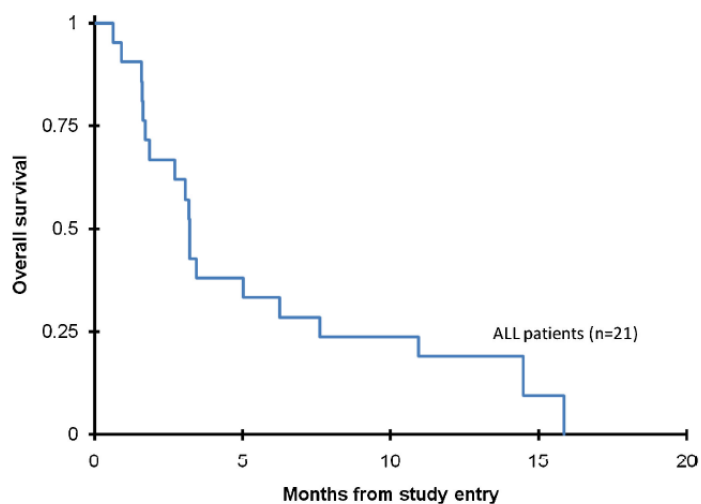
Figure 34 Kaplan-Meier curve for OS from Cooper *et al*. (2013)

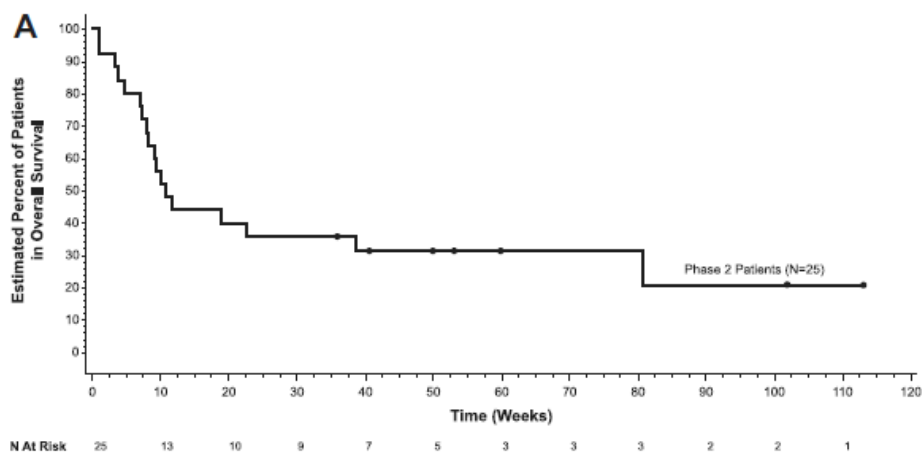**Figure 35 Kaplan-Meier curve for overall survival from Hijiya *et al*. (2011)**

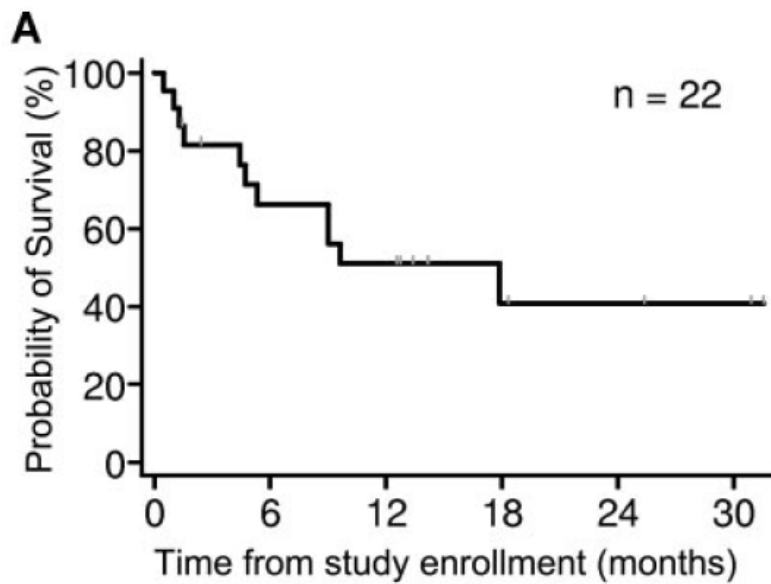**Figure 36 Kaplan-Meier curve for overall survival from Messinger *et al*. (2012)**

Figure 37 Kaplan-Meier curve for OS from Miano *et al*. (2012)