Single Technology Appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Novartis:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Response to additional clarification questions

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Anthony Nolan
   b. Blood Cancer UK
   c. Leukaemia Care
   d. NHS England

4. **Expert personal perspectives** from:
   a. Dr Sara Ghorashian – clinical expert, nominated by Novartis
   b. Professor Persis Amrolia – clinical expert, nominated by Anthony Nolan
   c. Sophie Wheldon – patient expert, nominated by Leukaemia Care
   d. Patient expert, nominated by Anthony Nolan

5. **External Assessment Report** prepared by the School of Health and Related Research, University of Sheffield

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]

Document B

Company evidence submission

October 2023

File name	Version	Contains confidential information	Date
ID6290_Tisagenlecleucel in rr B-cell ALL_Document B [NoCON]	Final	No	October 2023

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIEOP	Associazione Italiana di Ematologia e Oncologia Pediatrica
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic stem-cell transplant
AML	acute myeloid leukaemia
AS	Absolute shortfall
ATMP	Advanced Therapy Medicinal Products
BCR/ABL	Breakpoint cluster region/ Abelson
BIA	Budget Impact Analysis
BIC	Bayesian information criteria
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
CAA	Commercial Access Agreement
CAR-T	Chimeric antigen receptor T-cell receptor
CCLG	Children's Cancer and Leukaemia Group
CD3	Cluster of differentiation 3
CD19	Cluster of differentiation 19
CD22	Cluster of differentiation 22
CDF	Cancer Drugs Fund
CEC	Clofarabine, etoposide and cyclophosphamide
CER	Cost-effectiveness ratio
CHF	Swiss francs
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphoblastic leukaemia
CNS	Central nervous system
COVID-19	Coronavirus-19
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTL019	Tisagenlecleucel
CTCAE	Common Terminology Criteria for Adverse Events

DCA	Data Collection Agreement
DCO	Data cut-off
DFCI	Dana Farber Cancer Institute
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of remission
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External assessment group
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EQ-5D	European quality of life 5-Dimensions
EQ-5D-3L	European quality of life 5-Dimensions 3-Levels
EQ-VAS	EuroQol-visual analogue scales
ERG	Evidence Review Group
ESMO	European Society for Medical Oncolog
ESS	Effective sample size
EuroQol	European quality of life
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full analysis set
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, cytarabine, G-CSF and idarubicin
G-CSF	Granulocyte-colony stimulating factor
GEE	generalised estimating equation
GRACE	Good Research for Comparative Effectiveness
GVHD	Graft versus host disease
HAS	Haute Autorité de Santé
HBV	Hepatitis B virus
HCHS	Hospital and community health services
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplant
HSE	Health Survey for England
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient-level data
IRC	Independent review committee
ITC	Indirect treatment comparison

IV	Intravenous
IVIg	Intravenous immunoglobin
KM	Kaplan–Meier
LD	Lymphodepleting
LPLV	Last-patient last-visit
LTFU	Long-term follow-up
LYG	Life years gained
MAIC	Matching-adjusted indirect treatment comparison
MHC	Major histocompatibility complex
mITT	Modified intention-to-treat
MLL	Mixed lineage leukaemia
MRD	Minimal residual disease
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDRS	National Disease Registration Services
NE	Not estimable
NHB	Net health benefit
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NOK	Norwegian Krone
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NPC	National Product Code
NR	Not reported
NSSG	NHS Network Site Specific Group
ORR	Overall remission rate
OS	Overall survival
pALL	Paediatric acute lymphoblastic leukaemia
PAS	Patient access scheme
PBMC	Peripheral blood mononuclear cells
PD	Progressed disease
PedsQL	Paediatric quality of life questionnaire
PFS	Progression-free survival
PGS-CRS	Penn Grading Scale for CRS
Ph+ve	Philadelphia chromosome-positive
Ph-ve	Philadelphia chromosome-negative
PLL	Prolymphocytic leukaemia
PLN	Polish Zloty
PRO	Patient-reported outcome

PS	Proportional shortfall
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal social services research unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
r/r	Relapsed/refractory
RBC	Red blood cell
RCT	Randomised controlled trial
RFS	Relapse-free survival
RT-PCR	reverse transcription polymerase chain reaction
SAE	Serious adverse event
SCT	Stem cell transplant
SF-36	Short Form Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SOC	Standard of care
TA	Technology appraisal
TBI	Total body irradiation
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
UK	United Kingdom
UKALL	United Kingdom acute lymphoblastic leukaemia
US	United States
VOD	Veno-occlusive disease
VXLD	Doxorubicin
WBC	White blood cell
Wk	Week
WTP	Willing-ness to pay

Background

This is a Cancer Drugs Fund (CDF) exit submission for TA554: Tisagenlecleucel (Kymriah®) for the treatment of relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL) in people aged up to 25 years.[1] Key information from the initial appraisal is as follows:

- The primary source of evidence in the Data Collection Agreement (DCA) was the final data cut-off of the pivotal ELIANA trial.
- The confidential Commercial Access Arrangement (CAA) with National Health Service England (NHSE) comprised of a simple Patient Access Scheme (PAS) of [redacted] along with an additional rebate of [redacted] while in the CDF.
- The estimated eligible number of children and young adults treated is just 34 per year, reflecting the rarity of the condition.

This submission details updated clinical data from the ELIANA trial. These data demonstrate that median overall survival (OS) has still not been reached, despite median follow up of over 6 years. Both OS and event-free survival (EFS) data show clear plateaus in survival after 2 years, highlighting the potential for tisagenlecleucel to offer cure in a significant number of children. These results are further corroborated by real-world treatment effectiveness of tisagenlecleucel during the managed access period as captured in the NHSE CDF Report, which show even better OS results than the ELIANA trial.[2, 3] Given the high unmet need in this population of young children, Novartis is committed to working with the National Institute for Health and Care Excellence (NICE) and NHSE to ensure chimeric antigen receptor T-cell (CAR-T) therapy availability for this population in the UK.

The TA554 committee's preferred assumptions have been summarised in Table 1 below, alongside an overview of the company's approach in this submission to address the committee's concerns in TA554.

Table 1: Key committee assumptions in TA554

Area	Committee preferred assumptions	Company approach in this submission
Population	The committee in TA554 concluded that the company's positioning of tisagenlecleucel for Ph-ve disease based on clinical study eligibility was appropriate and acknowledged that patient numbers were too small for clinical- and cost-effectiveness in the population of patients with Ph+ve disease to be analysed separately.	The same positioning of tisagenlecleucel within this patient population has been retained in this managed access review submission.
Comparators	The committee concluded that whilst blinatumomab and salvage chemotherapy were both relevant comparators, blinatumomab was typically the preferred treatment option to bridge to subsequent allo-SCT.	Clinical expert feedback received as part of this updated submission indicates that blinatumomab remains the preferred treatment option, however salvage chemotherapy remains a relevant treatment option in patients not considered for treatment with blinatumomab.[4] As such, both

		comparators have been retained in this updated submission.
Long-term survival outcomes	Having acknowledged that survival estimates beyond 30 months were highly uncertain the committee concluded that with an assumed cure point of either 3 or 5 years, there was not robust evidence that tisagenlecleucel has a curative effect.	Long-term survival data has been collected as part of the latest data-cut off (17th Nov 2022) of the ELIANA trial, which reported at a median of 79.4 months. OS and EFS data both show clear plateaus in survival after two years, demonstrating the potential for tisagenlecleucel to offer a cure in a significant number of patients.[2] These longer-term survival results from the ELIANA trial are corroborated by longer-term survival data from the ENSIGN and B2101J trials, which showed similar long-term survival in patients treated with tisagenlecleucel.[2, 5, 6]
Uncertainty in the relative treatment efficacy of tisagenlecleucel	The company did a matching adjusted indirect treatment comparison to attempt to adjust prognostic factors in the pooled population of the 3 single-arm tisagenlecleucel studies to match those in the von Stackelberg *et al*. (2016) and Jeha *et al.* (2006) studies.[7, 8] A naive indirect treatment comparison (ITC) was also presented. The committee concluded that using a naive ITC was appropriate, but was subject to uncertainty as a result of the differences in the trial populations.	Novartis have updated the MAICs between tisagenlecleucel and both comparators, using long-term survival data from the ELIANA trial, as well as updated pooled ELIANA, ENSIGN and B2101J trial data.[2, 5, 6] Naive ITC results are also presented. The use of long term data reduces the uncertainty associated with these estimates.
Rates of subsequent allo-SCT	The committee concluded that the number of patients who would need an allogeneic stem cell transplant after tisagenlecleucel is highly uncertain.	Further clinical validation reflecting real-world use of tisagenlecleucel has confirmed that 25% of patients would be expected to receive a subsequent allo-SCT, which is very similar to the proportion in the ELIANA trial (22.78%).[2, 4] Real-world use of tisagenlecleucel during the managed access period, based on the NHSE CDF report confirmed that 12.28% of patients received a subsequent SCT.[3] This is explored as a scenario.
Treatment of B-cell aplasia with IVIg	The committee concluded that it was unknown how many patients would need IVIg treatment for B-cell aplasia and for how long.	Further clinical validation reflecting real-world use of tisagenlecleucel has confirmed that 75% of those with hypogammaglobulinaemia would receive IVIg treatment, which has been reflected in the base case cost-effectiveness analysis.[4]

Blinatumomab treatment costs	The committee favoured the assumption that patients would receive 2 cycles of blinatumomab.	Further clinical validation confirmed that two cycles of blinatumomab would be typically administered in NHS practice, which has now been incorporated in the company model.

Abbreviations: allo-SCT: allogenic stem cell transplant; CDF: Cancer Drugs Fund; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; IVIg: intravenous immunoglobin; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; EFS: event-free survival; TA: technology appraisal.
Source: NICE TA554 Committee Papers;[9] Jeha *et al.* 2006;[8] von Stackelberg *et al.* 2016;[7] ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] Novartis Data on File.[4]

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for tisagenlecleucel (Kymriah®) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse, hereafter referred to as relapsed/refractory (r/r) B-cell ALL.[10]

The decision problem addressed within this submission is broadly consistent with the NICE final scope for this appraisal with respect to the population, intervention, outcomes, and the NICE reference case. The comparators of relevance to this submission (fludarabine, cytarabine, granulocyte-colony stimulating factor [G-CSF] and idarubicin [FLAG-IDA] and blinatumomab) reflect those currently licensed and used in the patient population covered in this appraisal. A number of treatments listed in the NICE scope are not relevant to this appraisal, as they either do not reflect current NHS clinical practice, or are licensed and used in patient populations that differ from the target population for tisagenlecleucel. The differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 2.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Children and young adults up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse	As per NICE final scope
Intervention	Tisagenlecleucel	Tisagenlecleucel	As per NICE final scope
Comparator(s)	Established clinical management without tisagenlecleucel-T including: • fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy • clofarabine (off label) • inotuzumab ozogamicin (CD22-positive B-precursor ALL) • blinatumomab (Philadelphia-chromosome-negative ALL) • a tyrosine kinase inhibitor such as dasatinib, imatinib or ponatinib alone or in combination with FLAG-based combination chemotherapy (Philadelphia-chromosome-positive ALL) • SCT • Best supportive care (including palliative care)	• Salvage chemotherapy (specifically, FLAG-IDA [fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin]) • Blinatumomab	• The comparators of relevance to this submission reflect treatments currently licensed and used in the population of interest in this submission: patients under the age of 25 with ALL which is refractory, in relapse post-transplant, or in second or later relapse • Inotuzumab ozogamicin does not form a relevant comparator in this appraisal as it is not licensed for use in patients under 18, and is only recommended by NICE in adult patients with ALL.[11] Additionally, clinical feedback received as part of this appraisal suggests that inotuzumab ozogamicin is commonly used earlier in the treatment pathway, following first relapse, to a lesser extent in primary refractory patients and typically as a bridge to SCT or tisagenlecleucel).[4] Tisagenlecleucel is not licensed for use at first relapse (a population not covered by the scope of this appraisal),[10] whilst primary refractory patients only form a small part of the eligible patient population for tisagenlecleucel (only 7.6% of patients in the pivotal ELIANA trial had primary refractory disease).[12] The small proportion of patients with primary refractory disease in the ELIANA trial is representative of real-world clinical practice, as mentioned by clinical expert feedback received in TA554.[9] Clinical feedback also indicated that: ○ tisagenlecleucel is often reserved for use following

			treatment failure of inotuzumab ozogamicin in primary refractory patients,[4] and ○ inotuzumab ozogamicin is rarely considered a suitable treatment option for patients who have experienced a relapse post allo-SCT given the high risk of veno-occlusive disease (VOD)[4] • There is therefore limited overlap in the populations eligible for treatment with inotuzumab ozogamicin and tisagenlecleucel • SCT is used as consolidation therapy following complete remission with prior treatment, such as blinatumomab or salvage chemotherapy, and does not constitute a standalone treatment option. As such, a comparison to SCT alone is not appropriate. The benefits of SCT are already implicitly captured for modelled comparator treatments: trial data informing treatment benefit include a proportion of patients who received SCT subsequent to complete remission (where eligible). The costs of subsequent SCT are explicitly captured in comparator treatment costs. Patients receiving tisagenlecleucel can also receive SCT as a subsequent treatment (22.8% of patients in the ELIANA trial received a subsequent SCT), further precluding its consideration as a standalone comparator. SCT was not specified as a relevant comparator in the original submission for tisagenlecleucel in this indication (TA554), and its exclusion as a comparator in that submission was not raised as a key issue by the committee. Given its use in clinical practice has not changed (it is still used as consolidation following remission with a prior treatment), its exclusion as a comparator remains appropriate in this appraisal • The proportion of patients with Ph+ve ALL within the eligible patient population for tisagenlecleucel constitute a small minority (<3%)[13] and therefore tyrosine kinase

			inhibitors (TKIs) are not considered to represent relevant comparators to this submission, in line with TA554.[9] Furthermore, given the eligibility criteria of the tisagenlecleucel clinical trials, patients had to have tried and failed two prior lines of TKI therapy, and previous feedback from UK clinical experts is that the use of a 3rd TKI does not constitute standard practice[14] • Clinical feedback received as part of both the original submission (TA554) and this submission indicated that FLAG-IDA is the predominant chemotherapy regimen in patients with relapsed disease,[4, 14] being associated with similar remission rates to clofarabine, with lower toxicity. As such, clofarabine does not represent standard NHS practice in this indication, and is not considered a relevant comparator
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • response rate (including minimal residual disease and haematologic responses and complete remission) • rate of allogeneic stem cell transplant • adverse effects of treatment • health-related quality of life.	• Overall survival • Event-free survival • Relapse-free survival • Response rate (including minimal residual disease, haematological responses and complete remission) • Rate of allo-SCT • Adverse effects of treatment • Health-related quality of life (EQ-5D-3L and PedsQL)	N/A – in line with the final NICE scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per	The economic analysis will align with reference case stipulations as noted in the scope, however,	As noted in the case for change consultation document for the NICE methods of health technology evaluation, "NICE understands there is broad interest in potentially curative technologies including advanced therapy medicinal products

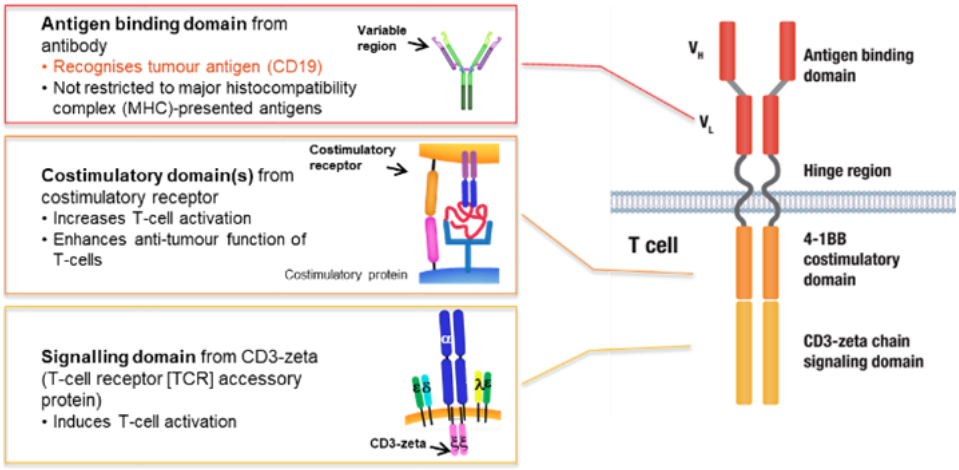
	quality-adjusted life year (QALY) • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	non-reference case discounting of 1.5% will also be considered.	(ATMP), and a policy-level drive to support them".[15] The report explored the use of a non-reference case discount of 1.5% for these technologies that have high upfront costs and long-term health benefits such as ATMPs and other one-off treatments. Furthermore, Section 4.5.3 of the NICE health technology evaluations manual (2022),[16] states that the "committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects if, in the committee's considerations, all of the following criteria are met: • The technology is for people who would otherwise die or have a very severely impaired life • It is likely to restore them to full or near-full health • The benefits are likely to be sustained over a very long period" Given tisagenlecleucel is an ATMP with curative potential, thus generating a large number of incremental QALYs (see Section B.3.9), and is a one-off treatment cost, consideration of a non-reference case discount of 1.5% is justified.

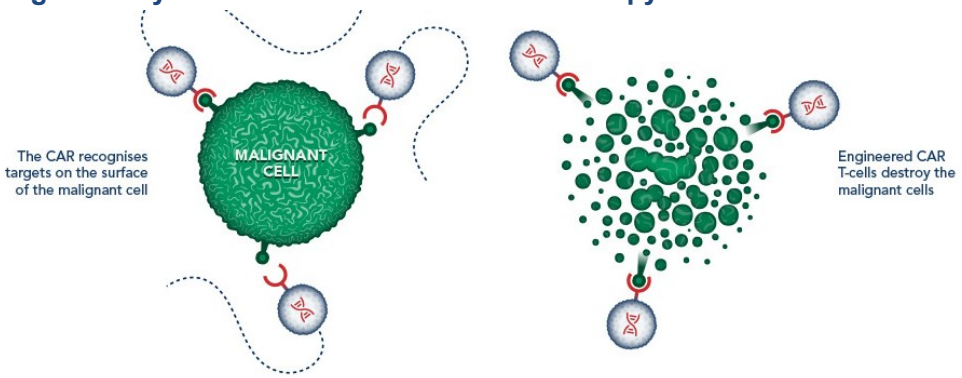
Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem cell transplantation; ATMP: advanced therapy medicinal products; CD22: cluster of differentiation-22; CDF: cancer drug fund; EQ-5D-3L: European quality of life 5-Dimensions 3-Levels; FLAG-IDA: fludarabine, cytarabine, G-CSF, and idarubicin; G-CSF: granulocyte-colony stimulating factor; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; PedsQL: Paediatric Quality of Life questionnaire; QALY: quality-adjusted life year; TA: technology appraisal; TKI: tyrosine kinase inhibitor; UK: United Kingdom; VOD: veno-occlusive disease.
Source: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]. Final Scope.[17]

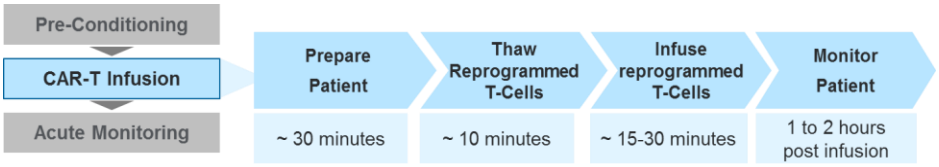
B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of tisagenlecleucel for r/r B-cell ALL is presented in Table 3.

Table 3: Technology being appraised

UK approved name and brand name	Tisagenlecleucel (Kymriah®)
Mechanism of action	Tisagenlecleucel is a genetically modified chimeric antigen receptor (CAR)-based autologous immunocellular therapy administered as a single intravenous (IV) infusion for the treatment of r/r B-cell ALL that utilises similar mechanisms to that of cytotoxic T-cells to kill leukaemic cells and thereafter maintain ongoing anti-tumour surveillance.[10] A patient's own T-cells are genetically engineered to express a CAR construct, which contains an external target-binding domain responsible for recognising leukaemic cells, and an internal activating domain which initiates T-cell activation (see Figure 1), allowing the induction of leukaemic cell death. As a second-generation CAR, tisagenlecleucel not only comprises the T-cell CD3ζ signalling domain, but has a co-stimulatory domain (4-1BB), in order to increase T-cell activation, anti-leukaemia activity and CAR-T-cell persistence.[10, 18] **Figure 1: Domains of the chimeric antigen receptor construct of tisagenlecleucel**  **Abbreviations:** CAR : chimeric antigen receptor ; MHC : major histocompatibility complex; TCR: T-cell receptor. **Source:** Novartis Pharmaceuticals UK Ltd. The underlying mechanism of action of tisagenlecleucel involves preferentially targeting the CD19 antigen, a glycoprotein with near-universal expression on B-cell precursors and B-cells.[19] Expression of CD19 is largely restricted to B lineage cells and is expressed in the majority of B-cell malignancies, including B-cell lymphomas.[18, 19] Tisagenlecleucel is therefore able to target tumour cells whilst largely sparing non-cancerous cells from cytotoxicity, consequently limiting systemic effects.[20] Once tisagenlecleucel binds to CD19-positive leukaemic cells, the CAR-T-cell becomes activated and the cytotoxic potential of these cells is realised (see Figure 2).[18] Death of malignant B-cells is primarily induced through CAR-mediated cytolysis (where target cells are killed due to destruction of the cell

	membrane), and the release of cytokines from the CAR-T cell.[21] Ligation of the CAR-T receptor also leads to CAR-T-cell proliferation.[21] **Figure 2: Cytotoxic mechanism of CAR-T therapy**  **Abbreviations:** CAR : chimeric antigen receptor. **Source:** Novartis Pharmaceuticals UK Ltd. By using the patients' own T-cells and their capacity for memory and surveillance, tisagenlecleucel acts as a 'living drug' that can provide an enduring response potentially over the course of a lifetime. As a patient-specific, single-dose, immunocellular gene-transfer therapy produced using pioneering technology, tisagenlecleucel was the first in this class of CAR-T therapy for the treatment of r/r B-cell ALL and represented a paradigm-shift in the treatment approach for this aggressive and potentially fatal disease that offered paediatric and young adult patients the potential for a cure with just a single infusion.
Marketing authorisation/ CE mark status	Tisagenlecleucel was issued an EU marketing authorisation for the treatment of paediatric and young adult patients with r/r B-cell ALL on 22nd August 2018.[22]
Indications and any restriction(s) as described in the SmPC	The EU marketing authorisation (EMA) wording for tisagenlecleucel in this indication is as follows: Tisagenlecleucel (Kymriah®) is "indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse."[22] Contraindications to treatment with tisagenlecleucel include hypersensitivity to the active substance or to any of the excipients listed in the SmPC. Contraindications of the lymphodepleting chemotherapy must also be considered.[10]
Method of administration and dosage	Tisagenlecleucel infusions should be administered in a qualified treatment centre by a healthcare provider experienced with immunosuppressed patients and trained for administration of tisagenlecleucel and management of patients treated with tisagenlecleucel. Tocilizumab and emergency equipment must be available prior to infusion of tisagenlecleucel and during the recovery period. Full details on the method of administration are provided in the SmPC (provided in Appendix C).[10] **Lymphodepleting chemotherapy:** Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1,000 cells/μL. Tisagenlecleucel is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000 cells/μL, then the patient should be re-treated with lymphodepleting

	chemotherapy prior to receiving tisagenlecleucel.[10] The recommended lymphodepleting chemotherapy regimen is:[10] • Fludarabine (30 mg/m^2 IV daily for 4 days) and cyclophosphamide (500 mg/m^2 IV daily for 2 days starting with the first dose of fludarabine) • Cytarabine (500 mg/m^2 IV daily for 2 days) and etoposide (150 mg/m^2 IV daily for 3 days starting with the first dose of cytarabine) *if the patient has experienced a previous grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemo-refractory state to a cyclophosphamide containing regimen administered shortly before lymphodepleting chemotherapy* **Pre-medication:** To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to tisagenlecleucel infusion. Corticosteroids should not be used at any time except in the case of a life-threatening emergency.[10] **Tisagenlecleucel infusion:** Treatment with tisagenlecleucel comprises a single-dose IV infusion of tisagenlecleucel at the following dosage: • For patients ≤50 kg: 0.2 to 5.0×10^6 CAR-positive viable T-cells per kg body weight • For patients >50 kg: 0.1 to 2.5×10^8 CAR-positive viable T-cells (non-weight based) The infusion should be administered 2 to 14 days after completion of the lymphodepleting chemotherapy at a rate of 10 to 20 mL per minute, adjusted as appropriate for small children and small volumes.[10] A summary of the tisagenlecleucel infusion process is presented in Figure 3 below. **Figure 3: Tisagenlecleucel infusion process**  **Abbreviations:** CAR-T: chimeric antigen receptor T-cell. **Source:** Novartis Pharmaceuticals UK Ltd.
Additional tests or investigations	Prior to infusion of tisagenlecleucel, the hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) status of the patient should be known.[10]
List price and average cost of a course of treatment	Tisagenlecleucel is associated with a one-off list price cost of £282,000.00.
Patient access scheme	There is an existing confidential (simple) patient access scheme (PAS) discount of [redacted]% on the tisagenlecleucel list price.

Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem-cell transplant; CAR: chimeric antigen receptor; CD3: cluster of differentiation 3; CD19: cluster of differentiation 19; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EU: European Union; GVHD: graft versus host disease; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IV: intravenous; MHC: major histocompatibility complex; r/r: relapsed/refractory; PAS: patient access scheme; SmPC: summary of product characteristics; TCR: T-cell receptor; UK: United Kingdom.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Disease overview

- ALL is an aggressive haematological malignancy, characterised by the overproduction and accumulation of immature white blood cells (lymphoblasts).[23] This causes the inhibition of normal blood cell production and function and leads to the infiltration of lymphoblasts to other organs.[23] ALL can develop extremely rapidly, and if untreated, can be fatal within weeks or months.
- Remission rates to conventional first-line chemotherapy are high (80–85%),[24, 25] however approximately 15–20% of patients will subsequently experience disease relapse.[26, 27] Rates of relapse remain relatively low following first relapse, however becoming increasingly common with each subsequent relapse.[28] A small proportion of patients do not respond to chemotherapy, either following first-line chemotherapy (primary refractory) or in the relapsed setting (chemo-refractory), for whom options are extremely limited[13, 29]
- For paediatric and young adult patients experiencing a second or greater relapse the prognosis is dismal; median OS from 3–7.5 months has been previously reported,[7, 8] and current treatment options are associated with poor remission rates, reduced HRQoL, as well as medical and psychosocial consequences.[21, 30, 31] For these patients, there is a critical unmet need for a routinely- funded therapy that can provide improved remission rates and the potential for a cure.

Epidemiology

- Despite being classified as a rare disease, incidence of ALL is highest in children and young adults, with over half of cases in patients aged <25 years, with incidence peaking in children aged 0–4.[32]
- ALL accounts for almost a third of all childhood cancers, and therefore represents a major contribution to the burden of paediatric cancer in the UK.[23]

Clinical pathway of care

- National clinical guidelines for the treatment of Ph-ve ALL patients aged up to 25 years are available in the UK from the Children's Cancer and Leukaemia Group (CCLG), and local guidelines are available for adult patients with ALL.[33, 34] However, guidelines for r/r disease are limited, and patients with r/r B-cell ALL in the UK are typically entered into experimental clinical trials if possible, with treatment informed by trial protocols and clinician judgement if not.[35]
- Based on feedback from UK clinical experts received as part of the original submission and this updated submission, ALL patients <18 years who experience a *first relapse* in the UK can be treated according to the ALLR3 trial protocol, however this is rarely used in this patient population.[4, 14] Blinatumomab is licensed for use in children in this patient population, with clinicians indicating that it is generally the preferred treatment option at this stage of disease, allowing for subsequent allo-SCT.
- Clinician feedback indicated that inotuzumab ozogamicin is also used within its licence for adult patients with r/r B-cell ALL at first relapse and for primary refractory disease, primarily as a bridge to allo-SCT, and in some cases prior to tisagenlecleucel. Given tisagenlecleucel is not licensed for use in patients with primary relapse, the primary refractory patient population is small, and a minority of patients eligible for tisagenlecleucel are aged over 18 years, there is limited overlap in the patient populations eligible for treatment with inotuzumab ozogamicin and tisagenlecleucel.
- If a *second relapse* occurs, treatment options are severely limited and prognosis is extremely poor. Treatment options may include blinatumomab or salvage chemotherapy (typically the FLAG-IDA regimen: fludarabine, cytarabine, granulocyte colony-stimulating factor [G-CSF] and idarubicin), with blinatumomab representing the preferred licensed treatment option for paediatric patients.[4]
- Tisagenlecleucel is positioned as a treatment option for paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. Given the critical unmet need in r/r B-cell ALL patients, tisagenlecleucel has already

become an established treatment option in this setting (reimbursed via the Cancer Drugs Fund [CDF]), providing a revolutionary and individualised approach with just a single infusion, and offering paediatric and young adult patients with r/r B-cell ALL the potential for a cure

B.1.3.1 Disease overview

ALL (also called acute lymphocytic leukaemia) is a rare haematological malignancy characterised by the overproduction and accumulation of cancerous, immature white blood cells (lymphoblasts) that originate within the bone marrow.[23] As an acute leukaemia, ALL is an aggressive disease that develops rapidly (within months) and is one of the most common cancers to affect children and young adults. This is in contrast to chronic lymphocytic leukaemia which develops more slowly (over years) and rarely affects children and young adults.[36, 37]

Disease categorisation

ALL can be further categorised according to the type of lymphocytes affected (B or T-cell) and the presence or absence of the Philadelphia (Ph) chromosome. [37, 38] B-cell ALL is considerably more common than T-cell ALL, representing 80% of cases in children.[39] In addition, the vast majority of patients have Ph-ve ALL, with just 3% of children suffering from Ph+ve disease, which is associated with a poorer prognosis, with high risk of relapse and refractory disease.[38, 40, 41] Patients with Ph+ve ALL follow a different treatment pathway than those with Ph-ve ALL. The licence for tisagenlecleucel covers all B-cell ALL patients regardless of Ph chromosome disease status. Subgroups will not be considered in this submission, consistent with the approach seen in the initial appraisal and accepted by the committee (TA554).[1]

Pathophysiology

The proliferation of lymphoblasts in patients with ALL causes the inhibition of normal blood cell production and function (red cells, white cells and platelets) and may eventually lead to the spread and infiltration of lymphoblasts to other organs, including the lymph nodes, liver, spleen, central nervous system (CNS) and testicles.[42] This rapid increase in cancerous lymphoblasts leads to the presentation of many non-specific symptoms indicative of reduced functional blood cell production, including fatigue, bruising, bone pain, fever, lymphadenopathy (swollen lymph nodes), infection and unusual and frequent bleeding.[26, 43] As an aggressive disease, if left untreated, ALL is usually fatal within a few weeks or months.[42]

Aim of treatment

The aim of treatment for paediatric and young adult patients with ALL at any stage of disease is to induce complete remission (CR).[44] For children and young adult patients who are diagnosed with ALL and are able to be treated, CR rates with conventional first-line chemotherapy are as high as 80–85%.[24, 25] However, despite these high remission rates, approximately 15–20% of patients will subsequently experience disease relapse, and the majority of relapses occur within two years of first-line treatment.[26, 27]

The aim of treatment for children and young adults who experience a first relapse is to achieve a second CR with the aim of, in most cases, enabling patients to receive an allogeneic stem cell transplant (allo-SCT) if they are eligible.[4, 14] Second CR rates with chemotherapy for patients who experience a first relapse are still reasonably high, and can range from 71–93%.[13] However, the chances of a patient achieving CR are substantially reduced with every subsequent relapse: CR rates for second, third and fourth or later relapse have been reported to be 44%, 27% and 12% respectively, demonstrating a substantial decrease in responsiveness with every treatment

failure.[28] The proportion of patients estimated to experience a second relapse is 36%.[45] This highlights the clinical burden in the relapsed setting, emphasising the urgent need for treatment options for patients who experience more than one disease relapse following conventional chemotherapy.

In addition to the morbidity and mortality associated with relapsed disease, a small proportion of patients may experience refractory disease, which can either be defined by a lack of CR after primary induction therapy for newly-diagnosed ALL (primary refractory) or a lack of CR after chemotherapy received in the relapsed setting (chemo-refractory).[29] Although rare (primary induction failure typically occurs in only 2–3% of patients), primary-refractory patients are severely limited in their options for successful treatment and remain a therapeutic challenge.[13]

Burden of disease

The burden of disease for ALL is associated with significant patient and parent/caregiver impact.[21, 30, 31, 46, 47] Patients with r/r B-cell ALL have an extremely poor prognosis and this is exacerbated further with each subsequent relapse.[46] Median overall survival (OS) with current treatment in the r/r setting have been reported to range from less than 3 months to 7.5 months.[7, 8] Unsurprisingly, r/r B-cell ALL survivors are even more likely to report poor general health, functional impairment, and activity limitations, respectively, compared with non-relapsed survivors.[48] The burden of disease is made worse by the fact that current treatments for r/r B-cell ALL are associated with poor clinical outcomes, poor HRQoL, and medical and psychosocial consequences.[21, 30, 31]

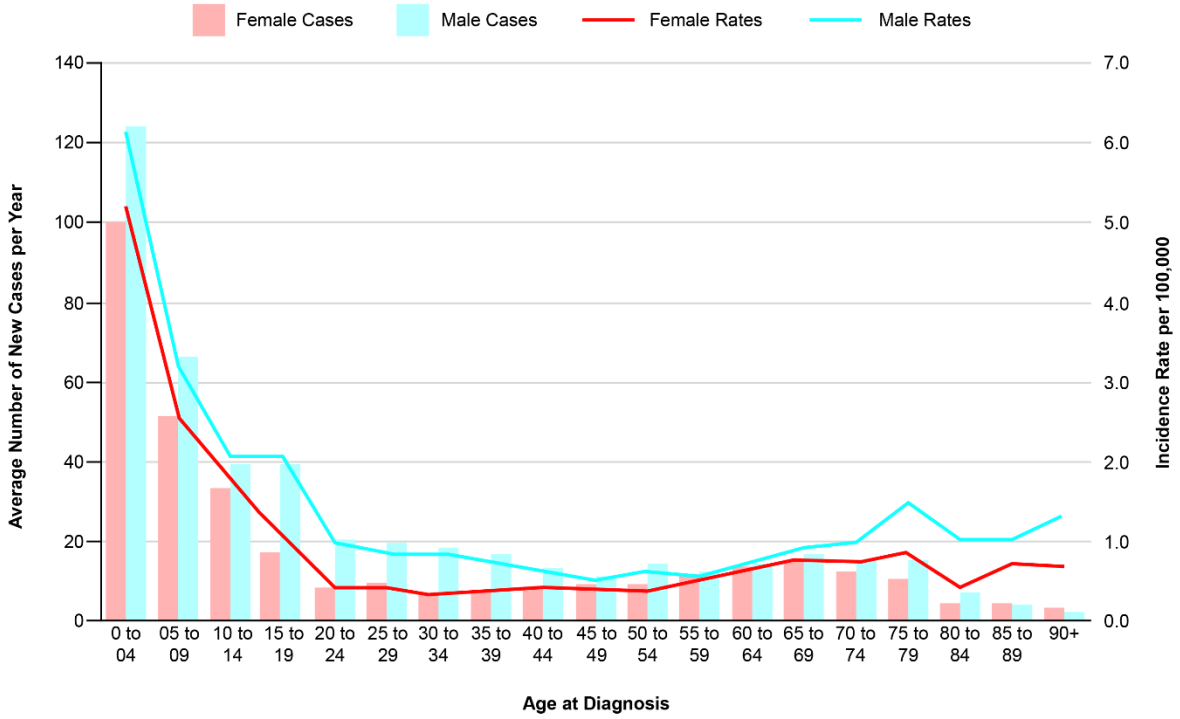
As a disease that affects children and young adults, who in some cases are very young, r/r B-cell ALL has a substantial impact on parents and caregivers, who can experience significant psychological distress, depression, anxiety, stress and emotional pressures.[31] Moreover, the economic burden of ALL can also be a major source of anxiety as regular inpatient and outpatient visits often disrupt parent and caregivers' employment and diminish their productivity.[49, 50] The burden of disease is therefore not only felt by patients themselves, but has a dramatic and widespread impact on entire families and their support networks.

The provision of a more effective treatment for r/r B-cell ALL that can offer substantial life extension and the potential for a cure, will help to alleviate this parent and caregiver burden, improving the quality of life of children and young adults affected by ALL. Clinical feedback received as part of this appraisal indicates that, following reimbursement via the CDF, tisagenlecleucel has already become an established treatment option for this patient population, reflective of its proven effectiveness in achieving long-term remission.[4]

Incidence of ALL in children and young adults

ALL is considered a rare disease, with 791 new cases of ALL diagnosed in the UK per year from 2016 to 2018, accounting for less than 1% of all new cancer diagnoses in adults and children in the UK.[32] However, the incidence of ALL is strongly related to age and, in stark contrast to most other cancers, ALL has the highest incidence in children and young adults, with the peak incidence in children aged 0–4 years old (see Figure 4).[32] Of the (average) 791 new cases of ALL diagnosed in the UK each year between 2016–2018, 497 cases (62.8%) were in patients aged 0 to 24 years. As such, although ALL is rare overall, the disease represents a major contribution to the burden of paediatric cancer in the UK, and accounts for 78% of all childhood leukaemia and almost one-third of all childhood cancers.[23]

Figure 4: Average number of new cases of ALL per year and age-specific incidence rates in the UK (2016–2018)



Abbreviations: ALL: acute lymphoblastic leukaemia; UK: United Kingdom.
Source: Adapted from Cancer Research UK.[32]

B.1.3.2 Clinical pathway of care

Tisagenlecleucel is licensed for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse.[22] The total number of children and young adults eligible for the use of tisagenlecleucel in the treatment of r/r B-cell ALL is estimated to be 34 per year. Further details on the calculation of the eligible patient population can be found in the budget impact analysis (BIA) of this submission.

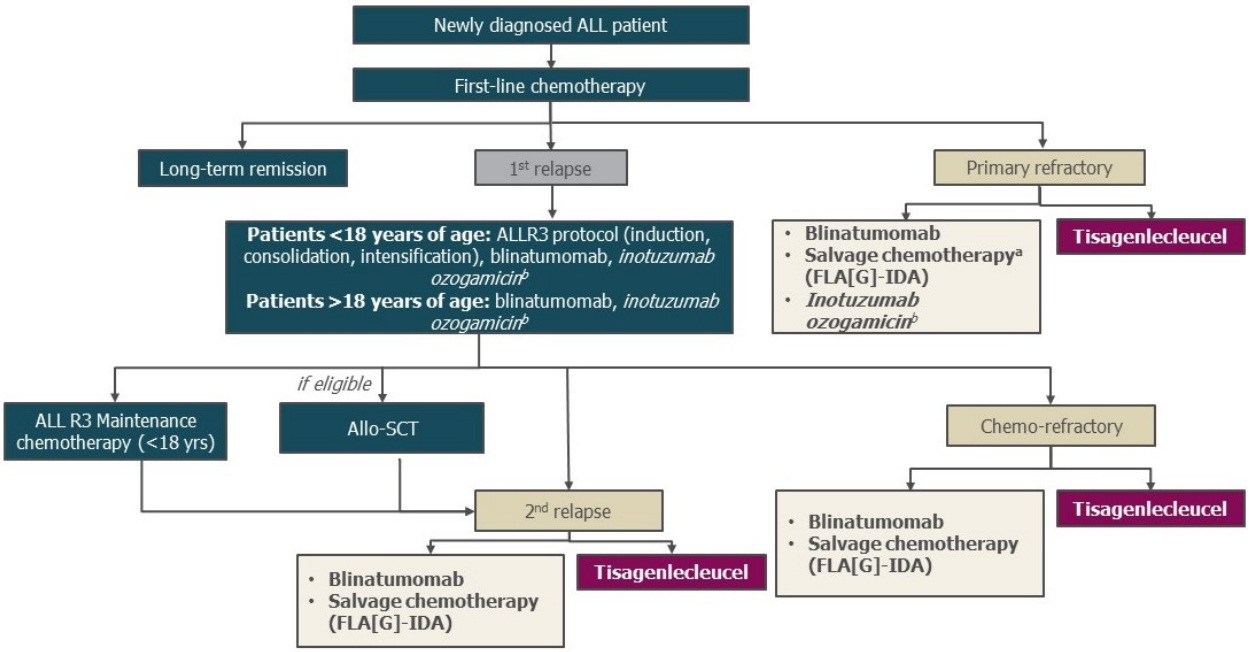
Clinical guidelines are available for adults from the European Society for Medical Oncology (ESMO) and for paediatric and young adult patients from the US National Comprehensive Cancer Network (NCCN) in the US.[51, 52] National clinical guidelines for the treatment of Ph-ve ALL patients aged up to 25 years are available in the UK from the Children's Cancer and Leukaemia Group (CCLG), and local guidelines are available for adult patients with ALL.[33, 34]

Paediatric and young adult patients with r/r B-cell ALL in the UK are typically entered into experimental clinical trials if possible.[35] For Ph-ve ALL patients who do not enter a clinical trial, and are aged between 1 to 25, first-line chemotherapy and primary refractory treatment is guided by CCLG UKALL 2019 Interim guidelines, and by clinician choice.[35] These guidelines do not include recommendations for patients in first relapse or for subsequent treatment lines. For patients aged less than 1, the UKALL 2019 Interim guidelines recommend these patients are treated according to the relevant Infant ALL protocol.[35]

The current treatment pathway for paediatric and young adult patients with B-cell ALL in the UK together with the potential positioning of tisagenlecleucel is summarised in

Figure 5 based on feedback from clinical experts in the UK consulted as part of this submission.[4]

Figure 5: Treatment pathway for ALL in the UK with the positioning of tisagenlecleucel



[a]Guidelines note that paediatric (<16 years) may be treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) protocol.[33] Patients typically receive FLA(G)-IDA, as per latest UK clinician feedback.[4] [b]Inotuzumab ozogamicin is not licensed for use in the paediatric population.
Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem cell transplantation; FLA[G]-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; NOPHO: Nordic Society of Pediatric Hematology and Oncology; Ph-ve: Philadelphia chromosome-negative.
Source: UK expert clinician feedback.[4]

Newly-diagnosed ALL

The aim of any treatment for paediatric and young adult patients with ALL at any stage of disease is to induce CR.[44] Standard first-line treatment for newly-diagnosed ALL in paediatric and young adult patients in the UK is multi-drug chemotherapy, which typically comprises a combination of three to four of the following drugs: dexamethasone, vincristine, asparaginase, daunorubicin, prescribed based on the patients' National Cancer Institute (NCI)-assessed risk level.[33] The chemotherapy treatment regimen consists of five phases: induction, consolidation, interim maintenance, delayed intensification and maintenance.[33] As per the CCLG UKALL 2019 interim guidelines, patients who achieve a CR following induction therapy would move on to receive maintenance chemotherapy or an allo-SCT (if eligible).[33]

Relapsed or refractory disease

Despite high CR rates that can be achieved with first-line chemotherapy, approximately 20% of patients have been reported to experience relapsed disease following CR from first-line chemotherapy.[25, 26] Guidelines note that the treatment of any patient with relapse should involve consideration of the maximum potential benefit that could be achieved, balanced against the risk of treatment-related morbidity and mortality.[34] The only curative approach to the treatment of relapse is allo-SCT, and thus the aim of treatment in this setting remains the achievement of a CR, which is a prerequisite for allo-SCT.[34]

First relapse (not included within the tisagenlecleucel licence or the target population for this submission)

For young adult patients who experience a first relapse, blinatumomab and inotuzumab ozogamicin are the preferred treatment options.[14, 34] Both blinatumomab and inotuzumab ozogamicin have been recommended by NICE for the treatment of adult patients with r/r B-cell ALL, in Ph-ve and CD22+ve patients, respectively (TA540 and TA541).[11, 53] Guidelines highlight that there are no head to head comparisons of either treatment in the relapsed setting, but both agents have a higher overall response rates, increased rates of MRD negativity and increase median OS compared to salvage chemotherapy and also increase the probability of receiving subsequent allo-SCT.[34] Blinatumomab and inotuzumab ozogamicin are offered as treatment options with the intention of bridging to allo-SCT, as per clinical feedback received for this appraisal.[4] The clinical feedback also highlighted the importance of consolidation with allo-SCT to ensure durable remissions, with event-free survival (EFS) otherwise estimated to be less than 20%.[4]

Patients under the age of 18 years who experience a first relapse in the UK can be treated according to the ALLR3 protocol, an international collaborative clinical trial protocol developed by the Childhood Leukaemia Working Party in the UK.[54] The ALLR3 protocol varies according to patient risk and contains three phases; induction, consolidation and intensification. For patients who achieve a CR following ALLR3 induction therapy, some patients will receive maintenance chemotherapy and some will go on to receive an allo-SCT (if eligible) (see

Figure 5). Feedback from clinical experts highlighted that blinatumomab is the preferred treatment option in paediatric patients with r/r B-cell ALL in England.[4] Whilst blinatumomab does not have a recommendation from NICE for treatment in the paediatric population, blinatumomab is licensed by the EMA for the treatment of paediatric patients over the age of 1 year and adults with r/r Ph-ve B-cell ALL.[55]

Primary refractory disease

Guidelines suggest that patients who experience primary refractory disease in the UK and are either over the age of 16 years or below the age of 16 years with ≥0.01% Minimal Residual Disease (MRD) at Week 14 of therapy are typically treated with blinatumomab, with the aim of bridging to allo-SCT (if patients are eligible).[33] Inotuzumab ozogamicin is also a treatment option in the primary refractory setting, within its licence for adult patients with r/r B-cell ALL, similarly used with the aim of bridging to allo-SCT (if patients are eligible) or as a bridge to subsequent treatment with tisagenlecleucel (reimbursed through the CDF). In the absence of blinatumomab or inotuzumab ozogamicin, patients may be treated with salvage chemotherapy, before receiving an allo-SCT if patients have achieved <0.1% MRD.[33] As indicated by feedback received from NHS England as part of the original submission for tisagenlecleucel (TA554), salvage chemotherapy in the primary refractory may consist of treatments based on the NOPHO protocol.[9] Additionally, clinical feedback to Novartis indicated that FLAG-IDA (fludarabine, cytarabine, G-CSF and idarubicin) may be used within the primary-refractory setting.[4] However, clinical feedback received as part of this submission indicated that only a minority of patients are treated with salvage chemotherapy in this setting.[4]

Second relapse or relapse post allo-SCT

For patients who experience a second relapse following maintenance chemotherapy or allo-SCT, or relapse before allo-SCT, treatment options are severely limited, and there is no established

protocol of care. Importantly, feedback from clinical experts consulted as part of this appraisal suggests that for patients who are in relapse post-transplant, or in second or later relapse, tisagenlecleucel (reimbursed through the CDF) has already become an established treatment option, reflecting its proven effectiveness in achieving long-term remission and the critical unmet need in this indication.[4] Alternative treatment options in this population are limited, but may include blinatumomab or salvage chemotherapy (typically FLAG-IDA) (see

Figure 5), with blinatumomab representing the preferred licensed treatment option for paediatric patients.[4] However, as indicated by clinical experts consulted for this appraisal, in patients who have experienced a relapse post allo-SCT, CAR-T therapy (i.e. tisagenlecleucel) is often favoured over blinatumomab given the high risk of allo-SCT toxicity, with approximately 50% of patients considered for tisagenlecleucel treatment having already received allo-SCT (in line with the ELIANA trial, where 60.8% had at least one prior SCT [Section B.2.3.3]).[4] Accordingly, inotuzumab ozogamicin is very rarely considered a suitable option for patients who have experienced a relapse post allo-SCT given the high risk of VOD.[4] Clinical experts consulted for this appraisal also highlighted that tisagenlecleucel is often favoured in patients who have chemo-refractory disease, given such patients may not achieve sufficient response on blinatumomab or inotuzumab ozogamicin to bridge to subsequent allo-SCT.[4]

Positioning of tisagenlecleucel

Tisagenlecleucel is positioned as a treatment option for paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse, in line with its licensed EMA marketing authorisation.[22] Therefore, within the context of this appraisal, blinatumomab and salvage chemotherapy (FLAG-IDA) represent the most relevant comparators to tisagenlecleucel within the treatment pathway for paediatric and young adult patients who have r/r B-cell ALL, in line with the comparators considered relevant in the original submission for tisagenlecleucel in this indication (TA554).[9]

Whilst clinical feedback indicated that inotuzumab ozogamicin is used in some patients with r/r ALL, it is not considered a relevant comparator to tisagenlecleucel in this appraisal, for several reasons:

- Inotuzumab ozogamicin has received a positive NICE recommendation for treatment in the adult r/r CD22+ve ALL patient population but has neither a recommendation from NICE nor a licence for treatment in the paediatric population.[11, 56] Whilst the licence for tisagenlecleucel includes patients aged up to 25 years, it is predominantly used in paediatric patients, as reflected by the mean age of 12 years in the principal trial (ELIANA) informing this submission.[12] Only a small proportion of patients in the ELIANA trial were ≥18 years old (17.7%).
- Feedback from clinical experts received as part of this update submission indicated that, within its licence for adult patients with r/r B-cell ALL, inotuzumab ozogamicin is commonly used earlier in the treatment pathway at first relapse, which does not form part of the licence for tisagenlecleucel or the target population for this submission.[4] This is corroborated by feedback from NHS England in the original submission for tisagenlecleucel (TA554) which indicated that, following its approval by NICE in the adult population, inotuzumab ozogamicin was expected to become the primary treatment option in the primary relapse and primary refractory settings.[9]

- Feedback from clinical experts received as part of this update submission confirmed that inotuzumab ozogamicin is also an important treatment option in the primary refractory setting.[4] However, this population represents only a small proportion of the patient population of relevance to this submission (only 7.6% of patients in the ELIANA trial had primary refractory disease). The small proportion of patients with primary refractory disease in the ELIANA trial is representative of real-world clinical practice, as mentioned by clinical expert feedback received in TA554.[9] In addition, inotuzumab ozogamicin is primarily used as bridging therapy to allo-SCT, and in some cases to subsequent treatment with tisagenlecleucel.
- Feedback from clinical experts received as part of this submission further highlighted that inotuzumab ozogamicin is rarely considered as a suitable treatment option for patients who have relapsed post-allo-SCT due to the high risk of VOD.[4] Clinical experts noted that without consolidation therapy (i.e. allo-SCT), patients have an extremely low EFS rates of less than 20%.[4]

Given inotuzumab ozogamicin lacks a licence in pALL and is commonly used as a treatment option at first relapse or in patients with primary refractory disease, there is very little overlap between the patient populations eligible for treatment with inotuzumab ozogamicin and tisagenlecleucel. Clinical feedback suggests that there is a place in UK clinical practice for both treatment options, but in different patient populations: inotuzumab ozogamicin primarily used as a bridge to allo-SCT or prior to tisagenlecleucel, and tisagenlecleucel (reimbursed through the CDF) already established as a treatment more broadly for patients who are in relapse post-transplant, or in second or later relapse. As such, inotuzumab ozogamicin does not represent a relevant comparator in this submission.

Limitations of current treatments and unmet need

Despite its use, there is no clinical evidence for the efficacy of FLAG-IDA in paediatric and young adult patients with r/r B-cell ALL. Consensus from four UK clinical experts was that expected median survival outcomes with FLAG-IDA are poor, and can be considered comparable to those observed with clofarabine monotherapy, which has been shown to be less than 3 months in this patient population and the rate of CR was 30%.[8, 14] The efficacy of blinatumomab has been studied in both paediatric patients (<18 years) and adults (>18 years) with r/r B-cell ALL; CR rates and median OS were very similar between the two populations.[7, 57] In paediatric patients, the CR rate for blinatumomab was 39% (95% CI: 27, 51%), with median OS only 7.5 months (95% CI: 4.0, 11.8 months); in adults, the rate of CR was 34% (95% CI: 28, 40%) with median OS 7.7 months (95% CI: 5.6, 9.6).[7, 57]

Given the limitations of current treatments in achieving CR and allowing for subsequent allo-SCT, tisagenlecleucel has become established as standard of care in UK clinical practice. Therefore, there is a critical unmet need for routine funding of this novel therapy that provides improved remission rates and extended survival for paediatric and young adult patients with r/r B-cell ALL. Tisagenlecleucel offers a revolutionary and individualised approach to meet this unmet need, providing children and young adults with r/r B-cell ALL the potential for a cure after only a single infusion. The clinical evidence for tisagenlecleucel in this patient population is compelling, and derives from three clinical trials with a total sample size of 239 patients (enrolled: 239; infused: 200). Across all three clinical trials, tisagenlecleucel has demonstrated consistent, clinically meaningful efficacy with high remission rates, deep molecular responses, and durable remissions. Of the three clinical trials, ELIANA is the pivotal trial being the largest multicentre

clinical trial. Full details of the results from all three tisagenlecleucel clinical trials are presented in Section B.2 of this submission.

B.1.4 *Equality considerations*

No equality issues related to the use of tisagenlecleucel are foreseen. People with ALL aged 26 years and above now have access to a CAR-T therapy via the CDF (TA893). [58] Routine commissioning of tisagenlecleucel would therefore ensure that people with ALL aged below 26 years have access to a CAR-T therapy option, independent of their age.

B.2 Clinical effectiveness

Clinical evidence

- ELIANA (NCT02435849), ENSIGN (NCT02228096) and B2101J (NCT01626495) are three completed studies which provide the key clinical evidence for the efficacy and safety of tisagenlecleucel for the treatment of paediatric and young adult patients with r/r B-cell ALL[59-61]
- Data from the latest data cut-offs (DCOs) for respective trials have been presented as part of this submission comprising of a total of 200 patients that have received tisagenlecleucel, of which 79 patients were from ELIANA, 64 from ENSIGN and 57 from B2101J.[2, 5, 6] ELIANA represents the pivotal clinical evidence being the largest multicentre trial, for which the latest DCO (17th Nov 2022) presents data with a median follow-up duration from infusion to the last patient last visit (LPLV) of 79.4 months

Efficacy

- The primary efficacy endpoint of ELIANA was met, with an independent review committee (IRC)-assessed overall remission rate (ORR) of 82.3% (65/79) (95% CI: 72.1, 90.0) 3 months after infusion.[2] Similarly, high remission rates were achieved in ENSIGN (ORR of 70.3%) and B2101J (ORR of 94.7%)[5, 6]
- A key secondary efficacy endpoint in the ELIANA trial was bone marrow minimal residual disease (MRD) negative complete remission/ complete remission with incomplete blood count recovery (CR/CRi) within 3 months post infusion.[2] This endpoint was met in 81.0% (95% CI: 70.6, 89.0) of patients, representing 98.5% of patients who achieved ORR demonstrating deep remission, confirming the observed clinical benefit seen with the primary endpoint.[2] Similarly, high ORRs with MRD-negative bone marrow remissions were reported in ENSIGN (67.2%) within 6 months post infusion and B2101J (86.0%) within 28 days post infusion[5, 6]
- In the majority of patients, durable remissions were observed across all three trials. The rate of event-free survival (EFS) at 12 months was 57.2% (95% CI: 44.5, 68.0) in ELIANA, 53.6% (95% CI: 39.3, 66.0) in ENSIGN and 57.8% (95% CI: 42.4, 70.4) in B2101J.[2, 5, 6] The rate of EFS at 60 months was 41.8% (95% CI: 29.1, 53.9) in ELIANA, 42.5% (95% CI: 27.7, 56.6) in B2101J.[2, 5, 6] The rate of EFS at 30 months was the latest follow-up point reported for ENSIGN (47.8% [95%CI: 33.0,61.1])[6]
- Median OS was not reached in ELIANA and 33/79 patients (41.8%) had died following tisagenlecleucel infusion.[2] The probability of survival at Month 6 was 88.6% (95% CI: 79.3, 93.9), 67.8% (95% CI: 56.1, 77.0) at Month 24 and 55.7% (95% CI: 43.6, 66.3) at Month 60.[2] ENSIGN had a median OS of 29.9 months, with the estimated probability of survival being 84.4% (95% CI: 72.9, 91.3) at Month 6 and 65.4% (95% CI: 52.4, 75.7) at Month 12.[6] B2101J had a median OS of 47.7 months, with the estimated probability of survival being 78.9% (95% CI: 65.9, 87.5) at Month 12 and 46.5% (95% CI: 30.8, 60.8) at Month 60[5]
- These results are further corroborated by real-world treatment effectiveness of tisagenlecleucel during the managed access period as captured in the NHSE CDF report, which show even better OS results than the ELIANA, ENSIGN and B2101J trials: median OS was not reached.[2, 3, 5, 6] OS at 6 months was 90% (95% CI: 82, 94), 12 months OS was 81% (95% CI: 73, 88), OS at 18 months was 78% (95% CI: 68, 85), OS at 24 months was 72% (95% CI: 62, 80) and OS at 36 months was 67% (95% CI: 55, 77).[3]

Summary of the results from the indirect treatment comparison

- In the absence of a head-to-head clinical trial evidence of tisagenlecleucel versus either blinatumomab or salvage chemotherapy (FLAG-IDA), a matched-adjusted indirect comparison (MAIC) was conducted for OS versus salvage chemotherapy (using clofarabine monotherapy as a proxy for the efficacy of FLAG-IDA) and blinatumomab, in line with the approach taken in the original submission for the treatment of r/r B-cell ALL in paediatric and young adult population (TA554)[9]
- Compared with blinatumomab and salvage chemotherapy, tisagenlecleucel was associated

with a longer OS for both the naïve comparison and MAIC performed

- Naïve comparison with blinatumomab (HR: 0.26 [95% CI: 0.16, 0.43]) and salvage chemotherapy (HR: 0.14 [95% CI: 0.09, 0.24])
- MAIC with blinatumomab (HR: 0.31 [95% CI: 0.18, 0.55]) and salvage chemotherapy (HR: 0.19 [95% CI: 0.10, 0.35])

Summary of safety results for tisagenlecleucel

- The safety profile of tisagenlecleucel has been well characterised and was consistent across all three trials.[2, 5, 6] AEs regardless of study drug relationship occurred in 100% patients in ELIANA, ENSIGN and B2101J[2, 5, 6]
- In the ELIANA trial, regardless of study drug relationship, the most frequent AEs overall were cytokine release syndrome (CRS), pyrexia, hypogammaglobulinaemia and decreased appetite, which occurred in at any grade in 77.2%, 44.3%, 40.5% and 38.0% patients, respectively.[2] CRS was also the most common AE regardless of study drug relationship in ENSIGN, followed by a decreased white blood cell count, hypogammaglobulinaemia and decreased neutrophil count. In B2101J, decreased white blood cell count was the most common AE regardless of study drug relationship, occurring in 94.7% patients. The next most common AEs were a decrease in haemoglobin, a decreased neutrophil count and CRS, occurring in 93.0%, 91.2% and 89.5% patient, respectively.[62] Of note, CRS was also identified as an adverse event of special interest (AESI) in the tisagenlecleucel trials
- SAEs post tisagenlecleucel infusion and regardless of study drug relationship were reported in 63 (79.7%), 52 (81.3%) and 52 (91.2%) patients in the ELIANA, ENSIGN and B2101J trials, respectively.[2, 5, 6] In all three trials, the most common SAEs regardless of study drug relationship were CRS, febrile neutropenia and hypotension occurring in 63.3%, 19.0% and 10.1% in ELIANA, 64.1%, 35.9% and 10.9% in ENSIGN and 82.5%, 71.9% and 38.6% in B2101J, respectively[2, 5, 6]
- A total of 33/79 (41.8%), 30/64 (46.9%) and 27/57 (47.4%) deaths occurred in ELIANA, ENSIGN and B2101J trials respectively post-tisagenlecleucel infusion[2, 5, 6]

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted in March 2018 with subsequent updates in July 2019 and March 2023 to identify relevant clinical evidence on the efficacy and safety of tisagenlecleucel for the treatment of paediatric patients with r/r B-cell ALL. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

The SLR included a total of 263 publications, reporting on 229 unique clinical trials of which 69 publications, reporting on 35 unique clinical trials were identified in the latest SLR update in March 2023. Of the 77 publications reporting on 66 unique trials identified in the SLR performed in March 2018, six publications reporting on three clinical trials were identified that investigated tisagenlecleucel in the patient population of interest for this appraisal: ELIANA [NCT02435849], ENSIGN [NCT02228096] and B2101J [NCT01626495]; see Section B.2.2. Four additional publications reporting on ELIANA [NCT02435849] were identified in the March 2023 update with no publications reporting on ENSIGN [NCT02228096] and B2101J [NCT01626495] identified.

B.2.2 *List of relevant clinical effectiveness evidence*

Three clinical trials were identified in the SLR that provide the key clinical evidence for the efficacy and safety of tisagenlecleucel for the treatment of paediatric and young adult patients with r/r B-cell ALL: ELIANA (NCT02435849), ENSIGN (NCT02228096) and B2101J (NCT01626495).[59-61]

ELIANA was an international, multicentre, phase II, single-arm, open-label study to determine the efficacy, safety and patient-reported outcomes of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL.[59] Data from ELIANA have been published by Laetsch *et al.* (2022) based on a median follow-up of 38.8 months from the date of infusion to data cut-off;[12] however, the publication does not present the most recent data cut from this trial. The most recent data cut-off (17th Nov 2022) of the ELIANA trial represents a median follow-up of over 6.5 years (79.4 months) from the date of infusion to LPLV.[2] Results for the final analysis of the primary endpoint (ORR) presented within this submission are taken from the final primary endpoint analysis (DCO 13th April 2018) and results for the remaining endpoints are taken from the ELIANA CSR (DCO 17th Nov 2022).[2, 63]

ENSIGN was a US-based, multicentre, phase II, single-arm, open-label study to determine the efficacy and safety of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL.[60] Data from ENSIGN have been published by Maude *et al.* (2016) representing a median 6.4 months of follow up;[64] however, as the publication does not present the most recent data cut from this trial, the data presented within this submission are taken from the ENSIGN CSR (DCO 24th May 2019 representing a median 31.7 months of follow up).[6]

B2101J was the first trial to be conducted in tisagenlecleucel and was a US-based, single-centre, phase I/IIa, single-arm, open-label study to determine the safety, tolerability and engraftment potential of tisagenlecleucel in patients with r/r B-cell ALL.[61] Data from B2101J have been published by Maude *et al.* (2014) representing a median 7 months of follow up;[65] however, as the publication does not present the most recent data cut from this trial, the data presented within this submission are taken from the B2101J CSR (DCO 7th May 2018 representing a median 47.2 months of follow up).[5]

An overview of the three tisagenlecleucel clinical trials ELIANA, ENSIGN and B2101J is provided in Table 3 below.

Table 4: Clinical effectiveness evidence

Study	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Study design	International, multicentre, phase II, single-arm, open-label study to assess efficacy, safety and patient-reported outcomes (PROs)	US-based, multicentre, phase II, single-arm, open-label study to assess efficacy and safety	US-based, single centre, phase I/IIa, single-arm, open-label study to assess the safety, tolerability and engraftment potential of tisagenlecleucel
Population	Paediatric and young adult patients (aged 3 years at screening to 21 years at initial diagnosis) with r/r B-cell ALL. N=97 **(enrolled)**; N=79 **(infused)**	Paediatric and young adult patients (aged 3 years at the time of screening to 21 years at the time of initial diagnosis) with r/r B-cell ALL and B-cell lymphoblastic lymphoma.[a] N=75 **(enrolled);** N=64 **(infused)**	Paediatric and young adult patients up to 24 years of age (range 1–24 years) with chemotherapy resistant or refractory CD19+ leukaemia and lymphoma.[a] N=67 **(enrolled; non-CNS3 ALL cohort);** N=57 **(infused; non-CNS3 ALL cohort][b]**
Intervention(s)	Single dose of tisagenlecleucel	Single dose of tisagenlecleucel	• Tisagenlecleucel administered as an IV

Study	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
	administered as an IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg body weight (for patients ≤50 kg) • 0.1 to 2.5×10^8 tisagenlecleucel cells (non-weight based) (for patients >50 kg)[c]	administered as a single IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) • 0.1 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg)[c]	infusion with intra-patient dose escalation: • Maximum total dose of 1.5×10^7 to 5×10^9 (0.3×10^6 to 1.0×10^8/kg) total cells (starting with a 10% fraction dose reduction but allowing for intra-patient dose escalation)
Comparator(s)	N/A – single-arm trial	N/A – single-arm trial	N/A – single-arm trial
Trial supports application for marketing authorisation	Yes	Yes	Yes
Trial used in the economic model	Yes	No	No
Reported outcomes specified in the decision problem	ORR, ORR with MRD-negative bone marrow, **EFS,** DoR, RFS, **OS,** Patient-reported outcomes (EQ-5D-3L), Safety	ORR, ORR with MRD-negative bone marrow, EFS, DoR, RFS, OS, Safety	ORR, ORR with MRD-negative bone marrow, EFS, DoR, OS, Safety

Bolded outcomes were included in the economic model.
[a]Note as of the respective data cuts presented within this submission for ENSIGN and B2101J trials, one patient with lymphoma had been infused with tisagenlecleucel in the B2101J trial. The populations treated and subsequently analysed within this submission exclusively include patients with r/r B-cell ALL.
[b]Reference to the patients in B2101J refers to the non-CNS3 cohort only and data for the non-CNS3 cohort only are presented within this submission.
[c]A target per-protocol dose of tisagenlecleucel transduced cells for paediatric patients consists of a single infusion of 2.0 to 5.0×10^6 transduced cells per kg body weight (for patients ≤50 kg) and 1.0 to 2.5×10^8 tisagenlecleucel transduced viable T-cells (for patients >50 kg). The following cell dose ranges here were infused if all other safety release criteria were met.
Abbreviations: ALL: acute lymphoblastic leukaemia; CD19: cluster of differentiation 19; CNS: central nervous system; DoR: duration of remission; EFS: event-free survival, EQ-5D-3L: European quality of life 5-Dimensions 3-Levels; IV: intravenous; MRD: minimal residual disease; N/A: not applicable; ORR: overall remission rate; OS: overall survival; RFS: relapse-free survival; r/r: relapsed/refractory; US: United States.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] Laetsch *et al.* (2022).[12]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

All three tisagenlecleucel clinical trials followed a similar trial design, with sequential phases of screening, enrolment, treatment (including apheresis, bridging chemotherapy, lymphodepleting chemotherapy and tisagenlecleucel administration) and follow-up.[2, 5, 6]

ELIANA trial design

ELIANA was an international, multicentre, phase II, single-arm, open-label study.[59] Paediatric and young adult patients with r/r B-cell ALL who were primary refractory, chemo-refractory, in 2nd or greater bone marrow relapse, relapsed after allo-SCT, or otherwise ineligible for allo-SCT were enrolled in the trial.[59]

A schematic of the ELIANA trial design is presented in Figure 6. The trial consists of several sequential phases: screening, pre-treatment, treatment and primary follow-up, secondary follow-up and survival follow-up.[2]

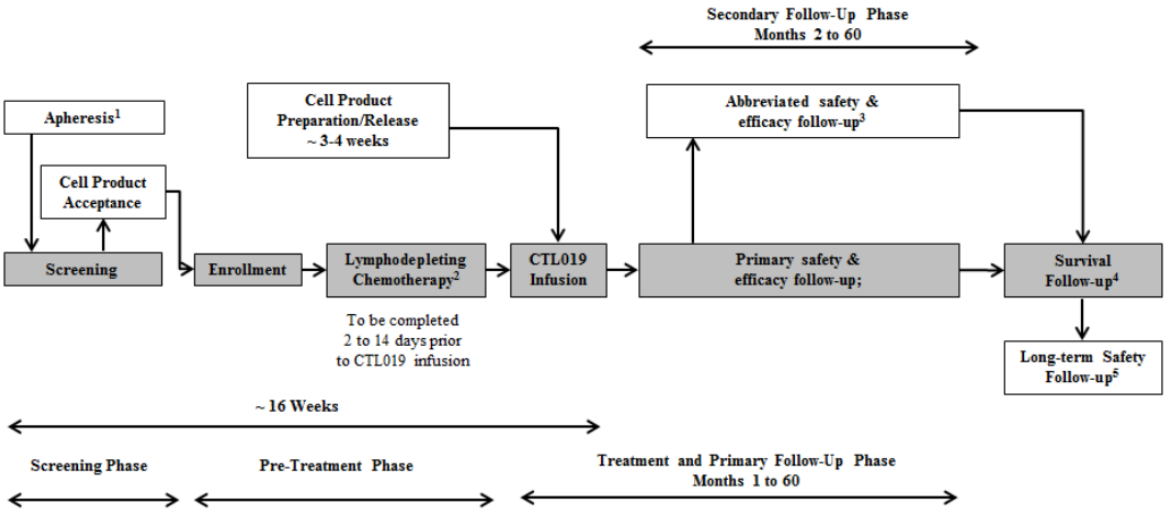
Screening and pre-treatment: Patients were screened for eligibility following leukapheresis. Eligible patients were then enrolled in the trial, and treated with bridging chemotherapy (where appropriate) followed by lymphodepleting chemotherapy 2–14 days prior to tisagenlecleucel infusion.

Treatment and primary follow-up: After tisagenlecleucel infusion, patients entered the primary follow-up period, during which efficacy was assessed monthly for the first six months, and then quarterly for up to 2 years and bi-annually for up to 5 years, or patient relapse.

Secondary follow-up: Patients could discontinue from primary follow-up due to reasons such as treatment failure, relapse after remission, pursuing allo-SCT while in remission or voluntary withdrawal. Patients who discontinued from the primary follow-up period before Month 60 continue to be followed in the secondary follow-up period for the collection of safety and survival data (every 3 months) for up to 5 years.

Survival and long-term safety follow-up: The survival follow-up period is to collect survival data (every 3 months) on patients who have completed the study up to 5 years post-tisagenlecleucel infusion. Patients will then continue to be followed as part of the long-term safety follow-up until 15 years post-tisagenlecleucel infusion.

Figure 6: ELIANA trial design



[1]Performed prior to study entry; [2]As indicated per protocol; [3]Only for patients who drop out of the primary follow-up before Month 60; [4]Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up; [5]Long-term safety follow-up conducted under a separate protocol.
Source: ELIANA CSR (DCO 17th Nov 2022).[2]

ENSIGN trial design

ENSIGN was a U.S based, multicentre, phase II, single-arm, open-label study to determine the efficacy and safety of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL.[60] Paediatric and young adult patients with r/r B-cell ALL or lymphoblastic lymphoma who were primary refractory, chemo-refractory, in 2nd or greater bone marrow relapse, relapsed after allo-SCT, or otherwise ineligible for allo-SCT were enrolled in the trial.[6] No patients with lymphoblastic lymphoma had been infused with tisagenlecleucel in the completed trial and therefore the population treated and subsequently analysed within this submission exclusively includes patients with r/r B-cell ALL. The ENSIGN trial design was identical to the ELIANA trial design and followed the schematic presented in Figure 6.[6]

B2101J trial design

B2101J was a U.S based single centre, phase I/IIa, single-arm, open-label study.[61] Paediatric and young adult patients with r/r B-cell ALL who were treatment refractory, relapsed after allo-SCT, or were otherwise ineligible for allo-SCT were enrolled in the trial.[61] The data presented within this submission only includes individuals from the B2101J cohort with non-CNS3 ALL who were analysed separately i.e. non-lymphoma patients and those without CNS relapse (<5 white blood cells [WBCs] per mL with leukaemic blast cells after cytocentrifugation following traumatic lumbar puncture), in line with the patient populations of ELIANA and ENSIGN.[66]

A schematic of the B2101J trial design is presented in Figure 7. The trial consists of several sequential phases: screening, treatment (consisting of apheresis, cytoreductive chemotherapy and tisagenlecleucel administration) and follow-up.[5]

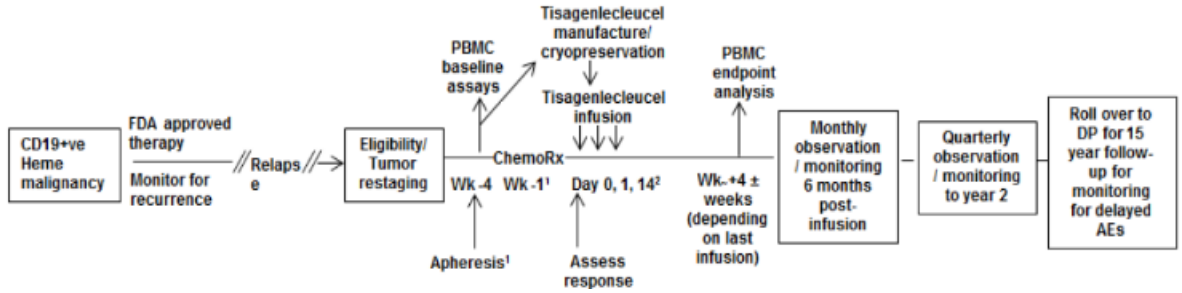
Screening and pre-treatment: Patients were screened for eligibility and eligible patients were then enrolled in the trial. Leukapheresis could occur prior to, or after enrolment. Patients were then treated with bridging chemotherapy (where appropriate) followed by lymphodepleting chemotherapy approximately one week prior to tisagenlecleucel infusion.

Treatment and primary follow-up: In B2101J, tisagenlecleucel infusion was administered in a dose-escalated manner, a minimum of 1–5 days after the completion of cytoreductive chemotherapy. After tisagenlecleucel infusion, patients entered the primary follow-up period, during which efficacy was assessed monthly for the first six months, and then quarterly for up to 2 years post-infusion.

Secondary follow-up: For patients who completed or prematurely discontinued from the primary follow-up phase while in remission, follow-up attempts were made to assess the patient's relapse, post-treatment antineoplastic therapy, and survival status until two years post the last patient infusion.

Survival and long-term safety follow-up: Once patients relapsed, they were followed for survival only. Patients completing or prematurely discontinuing participation in this study will then continue to be followed as part of the long-term safety follow-up until 15 years post-tisagenlecleucel infusion.

Figure 7: B2101J trial design



Abbreviations: AE: adverse event; DP: destination protocol; FDA: Food and Drug Administration; PBMC: peripheral blood mononuclear cells; Wk: week.
Source: B2101J CSR (DCO 7th May 2018).[5]

B.2.3.2 Trial methodology

A summary of the methodology of ELIANA, ENSIGN and B2101J is presented in Table 5. All three trials had a very similar study design, ALL patient population and methodology with the exception of the following minor differences. B2101J was a single-site study whereas ENSIGN and ELIANA were conducted across multiple sites.[59-61] The inclusion criteria for each trial were similar and although ENSIGN and B2101J allowed the inclusion of patients with lymphoma, the data presented within this submission are for patients with r/r B-cell ALL only.[2, 5, 6] The same target dose for tisagenlecleucel was followed in ELIANA and ENSIGN; as the first study of tisagenlecleucel in this indication, B2101J followed a dose-escalation regimen with a broader target dose range.[2, 5, 6]

Table 5: Summary of methodology of studies

Trial	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Location	**Clinical sites:** 25 centres across the US, EU (Austria, Belgium, France, Germany, Italy, Spain), Norway, Canada, Australia, and Japan **Manufacturing facilities:** Novartis Morris Plains manufacturing facility (US) and Fraunhofer Institut für Zelltherapie und Immunologie, Leipzig (Germany; referred to as the EU manufacturing facility)	**Clinical sites:** 13 centres across the US **Manufacturing facilities:** Clinical Cell and Vaccine Production Facility at the University of Pennsylvania and Novartis Morris Plains manufacturing facility	**Clinical site:** Children's Hospital of Pennsylvania in the US **Manufacturing facility:** Clinical Cell and Vaccine Production Facility at the University of Pennsylvania
Trial design	International, multicentre, phase II, single-arm, open-label study	Multicentre, phase II, single-arm, open-label study	Single centre, phase I/IIa, single-arm, open-label study
Eligibility criteria for participants	**Key inclusion criteria:** • Relapsed or refractory paediatric ALL with 2nd or greater bone marrow relapse **or** bone marrow relapse after allo-SCT **or** primary refractory/ chemo-refractory disease **or** Ph+ve disease if failed two lines of TKI therapy or if TKI contraindicated **or** ineligible for allogeneic allo-SCT • Age 3 at time of screening to age 21 at time of initial diagnosis • For relapsed patients, CD19 expression demonstrated in bone marrow or peripheral blood within 3 months of study entry • Adequate organ function • Bone marrow with ≥5% lymphoblasts by morphologic assessment at screening • Life expectancy >12 weeks • Karnofsky (age ≥ 16 years) or Lansky	**Key inclusion criteria:**[a] • Relapsed or refractory paediatric ALL or lymphoblastic lymphoma with 2nd or greater bone marrow relapse **or** bone marrow relapse after allogeneic allo-SCT **or** primary refractory/ chemo-refractory disease **or** Ph+ve disease if failed two lines of TKI therapy or if TKI contraindicated **or** ineligible for allogeneic allo-SCT • Age 3 at time of screening to age 21 at time of initial diagnosis • For relapsed patients, CD19 expression must be demonstrated in bone marrow or peripheral blood within 3 months of study entry • Adequate organ function • Bone marrow with ≥5% lymphoblasts by morphologic assessment at Screening • Life expectancy >12 weeks	**Key inclusion criteria:**[b] • ALL without curative options for therapy, including those not eligible for allo-SCT because of age, comorbid disease, other contraindications to TBI-based conditioning, lack of suitable donor, prior allo-SCT or declines allo-SCT (in CR3) as a therapeutic option ○ Patients may be in any complete response, or may have active disease but responding or stable after most recent therapy • **or** CD19+ follicular lymphoma **or** CLL **or** mantle cell lymphoma **or** B-cell PLL **or** CD19+ DLBCL or another high-grade NHL • Any relapse after prior allo-SCT will make patient eligible regardless of other prior therapy • Patients with relapsed disease after

	(age <16 years) performance status ≥ 50 at screening **Key exclusion criteria:** • Isolated extra-medullary relapse • Concomitant genetic syndromes associated with bone marrow failure states • Burkitt's lymphoma/leukaemia • Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease • Treatment with any prior gene therapy, anti-CD19/anti-CD3 therapy, or anti-CD19 therapy • Presence of grade 2–4 acute or extensive chronic GVHD • Active CNS3 involvement A full list of the inclusion and exclusion criteria is reported in the ELIANA CSR and is also presented in Appendix N.	• Karnofsky (age ≥ 16 years) or Lansky (age <16 years) performance status ≥ 50 at screening **Key exclusion criteria:** • Isolated extra-medullary relapse • Concomitant genetic syndromes associated with bone marrow failure states • Burkitt's lymphoma/leukaemia • Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease • Treatment with any prior gene therapy • Treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy • Presence of grade 2–4 acute or extensive chronic GVHD • Active CNS3 involvement A full list of the inclusion and exclusion criteria is reported in the ENSIGN CSR and is also presented in Appendix N.	prior allogeneic allo-SCT if no active GVHD and no immunosuppression • Adequate organ function • Life expectancy >12 weeks • Age 1–24 years **Key exclusion criteria:** • CNS3 disease that is progressive on therapy, or with CNS parenchymal lesions that might increase the risk of CNS toxicity • Treatment with any prior gene therapy • Presence of grade 2–4 acute or extensive chronic GVHD • A full list of the inclusion and exclusion criteria is reported in the B2101J CSR and is also presented in Appendix N.
Method of study drug administration	Single dose tisagenlecleucel administered as an IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) or • 0.1 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg) **Lymphodepleting regimen:** • Fludarabine (30 mg/m^2 IV daily for 4 doses) and cyclophosphamide (500 mg/m^2 IV daily for 2 doses starting	Single dose tisagenlecleucel administered as an IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) or • 0.1 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg) **Lymphodepleting regimen:** • Fludarabine (30 mg/m^2 IV daily for 4 doses) and cyclophosphamide (500 mg/m^2 IV daily for 2 doses starting with	• Tisagenlecleucel administered as an IV infusion with intra-patient dose escalation: • Maximum total dose of 1.5×10^7 to 5×10^9 (0.3×10^6 to 1.0×10^8/kg) total cells (starting with a 10% fraction dose reduction but allowing for intra-patient dose escalation) • Patients received one, two or (in one patient) three infusions

	with the first dose of fludarabine).	the first dose of fludarabine).	**Lymphodepleting regimen:** Fludarabine (30 mg/m^2 IV daily for 4 doses) and cyclophosphamide (500 mg/m^2 IV daily for 2 doses starting with the first dose of fludarabine).
Permitted and disallowed concomitant medication	Concurrent use of systemic steroids or immunosuppressant medications were prohibited except as required for physiologic replacement of hydrocortisone (or equivalent steroid) at physiological replacement doses of <12 mg/m^2/day, or in the case of a life-threatening emergency. Specifically, the following medications were prohibited: steroids, allogeneic cellular therapy, GVHD therapies, chemotherapy, CNS disease prophylaxis, radiotherapy, anti-T-cell antibodies. Full details of disallowed medications can be found within the ELIANA CSR.[2]	Concurrent use of systemic steroids or immunosuppressant medications were prohibited except as required for physiologic replacement of hydrocortisone (or equivalent steroid at physiological replacement doses of <12 mg/m^2/day), or in the case of a life-threatening emergency. Specifically, the following medications were prohibited: steroids, allogeneic cellular therapy, GVHD therapies, chemotherapy, CNS disease prophylaxis, radiotherapy, anti-T-cell antibodies. Full details of disallowed medications can be found within the ENSIGN CSR.[6]	Concurrent use of systemic steroids was prohibited with the exception of the use of inhaled steroids, or hydrocortisone for physiological replacement in patients with adrenal insufficiency.
Primary outcome *Outcomes not presented within this submission	• ORR determined by IRC assessment (defined as a best overall response [BOR] of either CR or CRi within 3 months of tisagenlecleucel administration)	• ORR determined by IRC assessment (defined as a BOR of either CR or CRi within 6 months of tisagenlecleucel administration)	• Safety and feasibility of administration of tisagenlecleucel • Duration of *in vivo* survival of tisagenlecleucel cells over time*
Key secondary outcomes *Outcomes not presented within this submission	• ORR (BOR of CR or CRi) with MRD negative bone marrow • DoR • RFS • EFS • OS • Patient-reported outcomes • Safety	• ORR with MRD negative bone marrow • DoR • RFS • EFS • OS • Safety • Percentage of patients who achieve CR or CRi at Month 6 without allo-SCT	• Anti-tumour response (ORR [defined as a BOR of CR or CRi] by local investigator assessment) • Cellular or humoral host immunity developed against the murine anti-CD19* • Safety and efficacy of tisagenlecleucel in patients with CNS3 disease* • Relative engraftment levels of

	• ORR determined by IRC assessment (defined as a BOR of either CR or CRi within 3 months of tisagenlecleucel administration) (US manufacturing facility only)* • BOR of CR or CRi with MRD negative bone marrow (US manufacturing facility only)* • Percentage of patients who achieve CR or CRi at Month 6 without allo-SCT between tisagenlecleucel infusion and Month 6 response assessment* • Percentage of patients who achieve CR or CRi and proceed to allo-SCT while in remission before Month 6 response assessment* • Disease response at Day 28±4 days* • Impact of baseline tumour burden on response* • Quality of response using MRD disease assessments before treatment and at Day 28±4 days after treatment* • Further secondary and exploratory outcomes are listed within the ELIANA CSR. Assessments of all endpoints are based on data from patients who received tisagenlecleucel manufactured by both manufacturing facilities unless specified differently	between tisagenlecleucel infusion and Month 6 response assessment* • Percentage of patients who achieve CR or CRi and then proceed to allo-SCT while in remission before Month 6 response assessment* • Disease response at Day 28±4 days* • Impact of Baseline tumour burden on response* • Further secondary and exploratory outcomes are listed within the ENSIGN CSR.	tisagenlecleucel TCRζ:4-1BB and TCRζ cells over time* • Tumour cell killing by tisagenlecleucel *in vitro** • Relative subsets of tisagenlecleucel (central memory, effector memory and regulatory T-cells)* Note that whilst the following outcomes are not stated explicitly as secondary outcomes of B2101J, the following outcomes are presented within this submission, in line with the ELIANA and ENSIGN trials: • ORR with MRD negative bone marrow • DoR • RFS • EFS • OS
Pre-planned subgroups	Pre-specified subgroup analyses for ORR, ORR with MRD negative bone marrow and DOR were performed based	Pre-specified subgroup analyses for ORR were performed on a number of baseline variables, including: age, gender, race,	Pre-specified subgroup analyses for ORR were performed on a number of baseline variables, including: age, gender, race,

	on a number of baseline variables, including: age, gender, race, ethnicity, prior allo-SCT, response status at study entry, baseline bone marrow tumour burden and baseline extramedullary disease presence.	ethnicity, prior allo-SCT, response status at study entry, baseline bone marrow tumour burden and baseline extramedullary disease presence.	ethnicity, prior allo-SCT, response status at study entry, baseline bone marrow tumour burden and baseline extramedullary disease presence.
Discontinuation of study treatment and premature patient withdrawal	• Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw or became lost to follow-up for any other reason • Patients were discontinued from primary follow-up due to treatment failure, relapse after remission, pursuing allo-SCT while in remission or voluntary withdrawal. Patients who discontinued during the primary follow-up period before Month 60 continued to be followed in the secondary follow-up period to collect safety data	• Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw or became lost to follow-up for any other reason • Patients were discontinued from primary follow-up due to lack of efficacy, new anticancer therapy, AEs death or voluntary withdrawal. Patients who discontinued during the primary follow-up period before Month 60 continued to be followed in the secondary follow-up period to collect safety data	• Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw or became lost to follow-up for any other reason • Patients who did not complete the study protocol were considered to have prematurely discontinued the study. For patients who completed or prematurely discontinued from the primary follow-up phase while in remission, follow-up attempts were made to assess the patient's relapse, post-treatment antineoplastic therapy, and survival status until two years post the last patient infusion. Once patients relapsed, they were followed for survival only
Duration of study and follow-up	• The study was initiated on 8th April 2015 and completed on 17th November 2022 • Primary and secondary follow-up consisted of the five years following infusion. The end of study is defined as the last patient's last visit, which is the last patient's Month 60 evaluation (or the time of premature withdrawal) • Patients will continue to be followed until 15 years post-infusion • **Data from the 17th November 2022**	• The study was initiated on the 14th August 2014 and completed on 24th May 2019 • Primary and secondary follow-up consisted of the five years following infusion. The end of study is defined as the last patient's last visit, which is the last patient's Month 60 evaluation (or the time of premature withdrawal) • Patients will continue to be followed until 15 years post-infusion • **Data from the 24th May 2019 data**	• The study was initiated on 15th March 2012 and completed on 7th May 2018 • Primary and secondary follow-up consisted of the two years following infusion • Patients will continue to be followed until 15 years post-infusion • **Data from the 7th May 2018 data cut-off** representing a median follow-up duration of 47.2 months are presented within this submission

	data cut-off representing **a** median duration from infusion of 79.4 months are presented within this submission	**cut-off** representing a median follow-up duration of 31.7 months are presented within this submission	

[a]As of the respective data cuts presented within this submission, no patients with lymphoma had been infused with tisagenlecleucel and therefore the ENSIGN population treated and subsequently analysed within this submission exclusively includes patients with r/r B-cell ALL. [b]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only. **Abbreviations:** ALL: acute lymphoblastic leukaemia; BCR/ABL: breakpoint cluster region Abelson; BM: bone marrow; BOR: best overall response; CAR: chimeric antigen receptor; CD3: cluster of differentiation 3; CD19: cluster of differentiation 19; CLL: chronic lymphoblastic leukaemia; CNS: central nervous system; CR: complete remission; CRi: complete remission with incomplete blood count recovery; CRF: case report form; DLBCL: diffuse large B-cell lymphoma; DoR: duration of remission; EFS: event-free survival; EU: European Union; FDA: Food and Drug Administration; GVHD: graft-versus-host disease; IRC: Independent Review Committee; LD: lymphodepleting; MLL: mixed lineage leukaemia; MRD: minimal residual disease; NHL: non-Hodgkin's lymphoma; ORR: overall remission rate; OS: overall survival; Ph+ve: Philadelphia chromosome positive; PLL: prolymphocytic leukaemia; RFS: relapse-free survival; RT-PCR: reverse transcription polymerase chain reaction; allo-SCT: stem cell transplantation; TBI: total body irradiation; TCR: T-cell receptor; TKI: tyrosine kinase inhibitor; US: United States.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] ClinicalTrials.gov.[61]

Description of outcomes reported in ELIANA, ENSIGN and B2101J

Definitions of the primary and key secondary outcomes assessed in ELIANA, ENSIGN and B2101J are provided in Table 6. ORR was the primary endpoint in ELIANA and ENSIGN, and was also assessed in B2101J. Key secondary outcomes reported across all three trials include EFS, DoR, RFS and OS.[2, 5, 6]

Table 6: Outcome definitions in ELIANA, ENSIGN and B2101J

Outcome	ELIANA	ENSIGN	B2101J
Primary outcome			
ORR	• ORR was defined as the proportion of patients with a BOR of CR or CRi during the 3 months after tisagenlecleucel administration as determined by IRC assessment • BOR was defined as the best disease response recorded from first tisagenlecleucel infusion until start of new anticancer therapy (including allo-SCT) • For a BOR to be categorised as CR or CRi, there had to be no clinical evidence of relapse at a minimum of 28 days after the initial achievement of CR or CRi	• ORR was defined as the proportion of patients with a BOR of CR or CRi during the 6 months after tisagenlecleucel administration as determined by IRC assessment. • BOR was defined as the best disease response recorded from first tisagenlecleucel infusion until start of new anticancer therapy (including allo-SCT). • For a BOR to be categorised as CR or CRi, there had to be no clinical evidence of relapse at a minimum of 28 days after the initial achievement of CR or CRi.	• ORR was defined as the proportion of patients with a BOR of CR or CRi as determined by local investigator assessment at the Day 28 visit. Disease assessment performed between study Day 2 to Day 59 and prior to the rescript of any new therapy was considered within the window. • BOR was defined as the best disease response recorded from first tisagenlecleucel infusion until death, lost to follow-up, relapse or start of new anticancer therapy.
Secondary outcomes			
Bone marrow MRD status	• Bone marrow MRD status was analysed using flow cytometry during the 3 months after tisagenlecleucel administration • The percentage of patients who achieved ORR with MRD negative bone marrow status was evaluated		
EFS	• EFS in all three trials was defined as the time from the date of first tisagenlecleucel infusion to the earliest date of death due to any cause, relapse or treatment failure • Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or a new anticancer therapy. In case of treatment failure, the event date was set to study Day 1 • In case a patient did not have relapse, death due to any cause or treatment failure prior to data cut-off, EFS was censored at the last adequate disease assessment date on or prior to the earliest censoring event (except for allo-SCT). EFS was censored if patients were: ○ Ongoing without an event ○ Lost to follow-up ○ Withdrew consent		

	○ New anticancer therapy ○ Adequate assessment was no longer available ○ Event after at least two missing scheduled disease assessments		
DoR	• DoR was defined as the duration from CR or CRi to the date of relapse or death due to underlying cancer • In case a patient did not have relapse or death due to underlying cancer prior to data cut-off, DoR was censored at the date of the last adequate disease assessment on or prior to the earliest censoring event (except for allo-SCT). DoR was also censored for the same reasons as above for EFS		
RFS	• RFS was defined as the time from CR or CRi to relapse or death due to any cause during CR or CRi • In case a patient did not have relapse or death due to any cause prior to data cut-off, RFS was censored at the date of the last adequate disease assessment on or prior to the earliest censoring event (except for allo-SCT). RFS was censored as above for EFS and DoR		
OS	• OS was defined as the time from date of first tisagenlecleucel infusion to the date of death due to any reason • Patients not known to have died at the data cut-off date were censored at their last contact date, which was defined as the latest date they were known to be alive		
Patient-reported outcomes			
EQ-5D	• European quality of life 5 dimensions (EQ-5D) was administered to measure health status for patients aged ≥ 8 years old at study entry • EQ-5D-3L was used for patients aged ≥ 13 years old at study entry while EQ-5D-Y was used for patients aged between eight and 12 at study entry	• N/A	• N/A
PedsQL	• Pediatric quality of life (PedsQL) questionnaire was used to measure health related quality of life for patients aged ≥ 8 years old at study entry	• N/A	• N/A

Abbreviations: AE: adverse event; allo-SCT: stem cell transplantation; BOR: best overall response; CR: complete remission; CRi: complete remission with incomplete blood count recovery; DoR: duration of remission; EFS: event-free survival; EQ-5D-3L: European quality of life 5-Dimensions 3-Levels; N/A: not applicable; ORR: overall remission rate; OS: overall survival; PedsQL: pediatric quality of life; RFS: relapse-free survival.
Source: ELIANA CSR (25th Apr 2017);[67] ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

B.2.3.3 Baseline characteristics

The ELIANA trial was initiated on 8th April 2015 (first patient first visit) and completed on 17th November 2022 (last patient last visit [LPLV]). 114 patients were screened, 97 patients were enrolled, and 79 patients had been treated with tisagenlecleucel.[2, 12] The 79 patients who received tisagenlecleucel infusion were aged between 3 to 24 years of age (mean 12.0 years), with fairly equal gender distribution (female, 43.0%).[12] The vast majority of patients had a Karnofsky/Lanksy performance status of greater than 70, with a median of 3.0 prior therapies of which 60.8% of patients had failed prior allo-SCT.[12, 68] The majority of patients had relapsed disease (92.4%) and 7.6% patients had primary refractory ALL.[2, 12]

The ENSIGN trial was initiated on 14th August 2014 (first patient first visit) and completed on 24th May 2019 (LPLV). 85 patients were screened, 75 patients were enrolled, and 64 patients had been treated with tisagenlecleucel.[6] The 64 patients who received tisagenlecleucel infusion were aged between 3 to 25 years of age (mean 12.4 years), with fairly equal gender distribution (female, 53.1%). All patients had a Karnofsky/Lanksy performance status of at least 50, with a median of 3 prior therapies of which 43.8% of patients had failed prior allo-SCT. The majority of patients had relapsed disease (89.1%) and 10.9% patients had primary refractory ALL.[6]

The B2101J trial was initiated on 15th March 2012 (first patient first visit) and completed on 7th May 2018 (LPLV). 67 patients were enrolled, and 57 patients had been treated with tisagenlecleucel.[5] The 57 patients who received tisagenlecleucel infusion were aged between 1 to 24 years of age (mean 11.6 years), with fairly equal gender distribution (female, 43.9%). All patients had a Karnofsky/Lanksy performance status of at least 80, 64.9% of patients had failed prior allo-SCT, and three patients had Ph+ve disease. The majority of patients had relapsed disease (94.6%) and 5.4% had primary refractory ALL.[5]

Baseline demographics, disease characteristics and a summary of disease history for the patients treated with tisagenlecleucel in ELIANA, ENSIGN and B2101J are presented in Table 7. The patient populations of each trial can be considered broadly similar and feedback from clinical experts in the treatment of ALL in the UK was that the study populations of each of the trials are reflective of the clinical population of paediatric and young adults patients with r/r B-cell ALL that would be candidates for tisagenlecleucel in the UK.[14] However, as noted by the Evidence Review Group (ERG) in the original submission for tisagenlecleucel in the treatment of r/r B-cell ALL (TA554), there are differences in Karnofsky/Lanksy performance status and number of patients who had not received a previous SCT.[9] Patients in the B2101J trial had higher Karnofsky/Lanksy performance status with 66.7% having a score of 100 compared to patients in the ELIANA and ENSIGN trials (38.0% and 28.1% respectively). Karnofsky/Lanksy performance status was identified by the ERG as a significant prognostic factor, thereby limiting the comparability of B2101J with ELIANA and ENSIGN.[9]

Table 7: Baseline characteristics (full analysis set)

Characteristic	ELIANA (full analysis set) (N=79)[a]	ENSIGN (full analysis set) (N=64)	B2101J (full analysis set) (N=57)[b]
Demographics			
Age (years)			
Mean (SD)	12.0 (5.4)	12.4 (5.2)	11.6 (5.1)
Median	11.0	12.5	11.0

Min–Max	3–24	3–25	1–24
Age category (years), n (%)			
<10	32 (40.5)	20 (31.3)	26 (45.6)
≥10 to <18	33 (41.8)	34 (53.1)	25 (43.9)
≥18	14 (17.7)	10 (15.6)	6 (10.5)
Sex, n (%)			
Female	34 (43.0)	34 (53.1)	25 (43.9)
Male	45 (57.0)	30 (46.9)	32 (56.1)
Race, n (%)			
White	58 (73.4)	52 (81.3)	48 (84.2)
Black	N/A	N/A	4 (7.0)
Asian	10 (12.7)	5 (7.8)	2 (3.5)
Pacific Islander	N/A	N/A	1 (1.8)
Other	11 (13.9)	7 (10.9)	2 (3.5)
Ethnicity, n (%)			
Hispanic or Latino	15 (19.0)	25 (39.1)	5 (8.8)
Mixed Ethnicity	N/A	N/A	2 (3.5)
Other	64 (81.0)	39 (60.9)	50 (87.7)
Weight for tisagenlecleucel manufacturing (kg)			
Mean (SD)	41.9 (23.3)	43.7 (20.1)	40.2 (19.1)
Median	35.1	42.4	37.1
Min-Max	14.4–137.0	16.2–93.4	11.1–117.0
Karnofsky/Lanksy performance status, n (%)			
100	30 (38.0)	18 (28.1)	38 (66.7)
90	23 (29.1)	28 (43.8)	10 (17.5)
80	13 (16.5)	13 (20.3)	5 (8.8)
70	8 (10.1)	2 (3.1)	3 (5.3)
60	2 (2.5)	1 (1.6)	N/A
50	3 (3.8)	2 (3.1)	N/A
<50	N/A	0	N/A
Missing	N/A	N/A	1 (1.8)
Disease history and prior therapies			
Diagnosis of disease, n (%)			
B-cell ALL	79 (100.0)	64 (100.0)	56 (98.2)
T-cell ALL	N/A	N/A	1 (1.8)
Age at initial diagnosis (years)			
Mean (SD)	7.5 (5.0)	8.6 (5.3)	NR
Median	6.0	8.0	NR
Min-Max	0–21	1–19	NR
Prior haematopoietic stem cell transplant (SCT)			
0	31 (39.2)	36 (56.3)	20 (35.1)
1	42 (53.2)	26 (40.6)	35 (61.4)
2	6 (7.6)	2 (3.1)	2 (3.5)

Disease status, n (%)			
Primary refractory	6 (7.6)	7 (10.9)	3 (5.3)
Chemo-refractory	73 (92.4)	57 (89.1)	54 (94.7)
Relapsed disease			
Number of previous lines of therapy, n (%)			
Mean (SD)	3.5 (1.6)	2.9 (1.5)	NR
Median	3.0	3.0	NR
Min-Max	1–8	1–9	1–8
Time since initial diagnosis to first relapse (months)[d]			
n	73	56	NR
Mean (SD)	32.9 (16.6)	33.6 (23.8)	NR
Median	32.9	27.6	NR
Min-Max	1.0–70.0	1.0–108.0	NR
Time since initial diagnosis to first relapse category (months), n (%)[d]			
<18	16 (21.9)	16 (28.1)	NR
18 to 36	25 (34.2)	18 (31.6)	NR
>36	32 (43.8)	22 (38.6)	NR
Not applicable	NA	1 (1.8)	NR
Time since most recent relapse to tisagenlecleucel infusion (months)[d]			
n	73	57	54
Mean (SD)	4.2 (2.7)	3.1 (1.7)	5.8 (3.1)
Median	3.5	2.6	5.1
Min-Max	1.5–13.8	1.3–9.8	1.3–20.5

[a] Data for disease history and prior therapies received by patients in ELIANA have been derived from ELIANA CSR (13th Apr 2018).[63]
[b] Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only
[c] This value for B2101J is for patients receiving >1 prior allo-SCT, rather than exactly two
[d] Calculated for relapsed patients only
Abbreviations: allo-SCT: stem cell transplantation; ALL: acute lymphoblastic leukaemia; CNS: central nervous system; MRD: minimal residual disease; N/A: not applicable; NR: not reported; SCT: stem cell transplantation; SD: standard deviation.
Source: ELIANA CSR (17th Nov 2022);[2] ELIANA CSR (13th Apr 2018);[63] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] Laetsch *et al.* (2022).[12]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Definitions of the key study populations analysed from ELIANA, ENSIGN and B2101J are presented in Table 8. Assessments of all endpoints were based on data from patients who received tisagenlecleucel (i.e. the full analysis set for efficacy endpoints, and the safety set for safety endpoints). The numbers of patients in each analysis set are presented in Table 9.

Table 8: Analysis set definitions

	ELIANA	ENSIGN	B2101J
Screened set	All patients who had signed informed consent/assent and were screened in the study		
Enrolled set	All patients who were enrolled in the study. Enrolment date was defined as the point at which the patient met all inclusion/exclusion criteria, and the patients' leukapheresis product was received and accepted by the manufacturing facility		All screened patients who met all inclusion/exclusion criteria excluding screen failure patients and patients in screening at the time of data cut-off
Full analysis set	All patients who received infusion of tisagenlecleucel		
Efficacy analysis set	All patients who received infusion of tisagenlecleucel at least 6 months prior to the data cut-off	All patients who received infusion of tisagenlecleucel at least 6 months prior to the data cut-off	N/A[a]
Safety set	All patients who received infusion of tisagenlecleucel		

[a]There was no requirement for an efficacy analysis set in B2101J, hence the FAS was used for all outcomes.
Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system; FAS: full analysis set; N/A: not applicable.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

Table 9: Trial populations used for the analysis of outcomes of relevant clinical trials

Analysis set, n (%)	ELIANA	ENSIGN	B2101J[a]
Screened set	114 (100)	85 (100)	-
Enrolled set	97 (85.1)	75 (88.2)	67 (100)
Full analysis set	79 (69.3)	64 (75.3)	57 (85.1)
Efficacy analysis set[b]	79 (69.3)	64 (75.3)	-
Safety set	79 (69.3)	64 (75.3)	57 (85.1)

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b]The efficacy analysis set was used only for outcomes related to ORR in ENSIGN. There was no requirement for an efficacy analysis set in B2101J, hence the FAS was used for all outcomes.
Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system; DOR: duration of remission; FAS: full analysis set; ORR: overall remission rate.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

The statistical analyses used for the primary endpoints of the ELIANA, ENSIGN and B2101J trials alongside sample size calculations and methods for handling missing data, are presented in Table 10.

Table 10: Statistical methods for the primary analysis of relevant clinical trials

Trial name	ELIANA	ENSIGN	B2101J
Hypothesis objective	Null hypothesis: ORR ≤20% during the 3 months after tisagenlecleucel administration Alternative hypothesis: ORR >20% during the 3 months after tisagenlecleucel administration	Null hypothesis: ORR ≤20% during the 6 months after tisagenlecleucel administration Alternative hypothesis: ORR >20% during the 6 months after tisagenlecleucel administration	• The statistical analysis will be primarily descriptive in keeping with the exploratory nature of the study. All adverse events will be described and exact 95% confidence intervals will be produced for adverse event rates, both overall and within major categories. The change in the ratio of tisagenlecleucel cells over time will be compared using a Wilcoxon signed-rank test for paired data[5] • Analysis of other secondary endpoints such as anti-tumour activity will also be primarily descriptive and may include summary statistics such as means and standard deviations or Kaplan–Meier curves for survival information[5]
Statistical analysis	The ORR was summarised along with the 2-sided exact Clopper-Pearson CIs with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan and DeMets (1983) as implemented in East 5.4. The study was considered successful if the lower bound of the 2-sided exact CI for ORR was >20%, so that the null hypothesis could be rejected		
Sample size, power calculation	• In a previous study of clofarabine in patients with r/r B-cell ALL who had had 2 or more prior regimens, the reported ORR was 20% (95% CI: 10, 34).[8] Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level was considered to indicate meaningful efficacy in this highly refractory population[67] • Based on the null and alternative hypotheses, 76 patients in the FAS would provide >95% power to demonstrate statistical significance at one-sided cumulative 0.025 level of significance, if the underlying ORR was 45%. In this setting, an	• Although the study enrolled both ALL patients and lymphoblastic lymphoma patients, the sample size calculation was primarily based on the hypothesis testing for ALL patients • In a previous study of clofarabine in patients with relapsed or refractory B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20% (95% CI: 10, 34).[8] Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy in this highly refractory population[6] • Based on the null hypothesis of ORR ≤20% and alternative hypothesis of ORR >20%, 45 ALL patients in the FAS provided 93% power to demonstrate statistical significance using a 2-look Lan-Demets group sequential design with	B2101J is a phase I/IIa study and the dropout rate was anticipated to be approximately 20%.[5] If this exploratory study suggested that one vector persists and engrafts better than the other vector, then a larger follow-on trial was to be designed that had the statistical power to assess the potential efficacy of that vector (hence the development of the ENSIGN and ELIANA trials)[5]

	ORR of 30% (=23/76) would be needed to claim success[67] • Within the expected sample size of 76 patients infused with tisagenlecleucel, at least 10 patients were to be treated with tisagenlecleucel from the EU manufacturing facility. If there were at least 6 patients among them who achieved BOR of CR or CRi, the lower bound of the 95% CI would be higher than 20%[67] • The actual number of patients to be enrolled depended on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients would not be infused, approximately 95 patients were needed to be enrolled to reach the number of patients required[67]	O'Brien-Fleming type boundary at one-sided overall 0.025 level of significance, if the underlying ORR is 45%. In this setting, an ORR of 34% (17/50) was needed to claim success[6] • It was anticipated that the lymphoblastic lymphoma population was small and would represent less than 10% of the entire population. Therefore with 50 patients treated in the study, it was assumed that 45 ALL patients would be treated[6] • The actual number of patients enrolled depended on the pre-infusion dropout rate. Limited data were available to provide robust estimate on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients were not infused due to reasons such as tisagenlecleucel product manufacturing issues, worsening of patient's condition, etc., 63-67 patients were estimated to be enrolled to ensure 50 patients are treated[6]	
Data management, patient withdrawals	• Patients in the study with unknown clinical response were considered non-responders[67] • Where there were missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" was assigned unless at least one observation was made, which qualified for relapse. Relapse could have been determined by the relapsed component alone[67] • Other missing data were noted as missing where applicable[67]	• Patients in the study with unknown clinical response were considered non-responders[6] • Where there were missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" was assigned unless at least one observation was made, which qualified for relapse. Relapse could have been determined by the relapsed component alone[6] • Other missing data were noted as missing where applicable[6]	• Patients in the study with unknown clinical response were considered non-responders[5] • Where there were missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" was assigned unless at least one observation was made, which qualified for relapse[5] • Other missing data were noted as missing where applicable[5]

Abbreviations: CR: complete remission; CRi: complete remission with incomplete blood count recovery, IRC: Independent Review Committee; ORR: overall remission rate.
Source: ELIANA CSR (25th Apr 2017);[67] ELIANA CSR (31st Dec 2017);[68] ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

An overview of the quality assessments of ELIANA, ENSIGN and B2101J performed as part of the March 2018 original SLR for the original submission (TA554) is presented below. These quality assessments were performed for the data extraction based on the Good Research for Comparative Effectiveness (GRACE) checklist for the methodological quality of randomised and non-randomised studies of health care interventions, and indicate that all three trials can be considered to be of good quality.[69] The clinical effectiveness evidence were however, extracted from the respective trial CSRs which contained data from the latest data-cut.

Table 11: Overview of the quality assessment of ELIANA, ENSIGN and B2101J based on the GRACE checklist

Question	ELIANA	ENSIGN	B2101J
Data			
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)? Note: not all details of treatment are required for all research questions	Yes	Yes	Yes
D2. Were the primary outcomes adequately recorded for the study purpose (e.g., available in sufficient detail through data sources)?	Yes	Yes	No
D3. Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment (e.g., opinion about whether the patient's condition has improved)?	Yes	Yes	No
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	Yes	Yes	Yes
D5. Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/intervention group and the comparison group?	N/A[a]	N/A[a]	N/A[a]
D6. Were important covariates that may be known confounders or effect modifiers available and recorded? Important covariates depend on the treatment and/or outcome of interest (e.g., body mass index should be available and recorded for studies of diabetes; race should be available and recorded for studies of hypertension and glaucoma).	Yes	Yes	Yes
Methods			
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment? Efforts to include only new initiators may include restricting the cohort to those who had a washout period (specified period of medication nonuse) before the beginning of study follow-up.	Yes	Yes	Yes
M2. If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	N/A[a]	N/A[a]	N/A[a]
M3. Were important confounding and effect-modifying variables taken into account in the design and/or	No	No	No

analysis? Appropriate methods to take these variables into account may include restriction, stratification, interaction terms, multivariate analysis, propensity score matching, instrumental variables, or other approaches.			
M4. Is the classification of exposed and unexposed person-time free of "immortal time bias," i.e., "immortal time" in epidemiology refers to a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur.	Yes	Yes	Yes
M5. Were any meaningful analyses conducted to test key assumptions on which primary results are based (e.g., were some analyses reported to evaluate the potential for a biased assessment of exposure or outcome, such as analyses where the impact of varying exposure and/or outcome definitions was tested to examine the impact on results)?	Yes	Yes	No

[a]N/A as ELIANA, ENSIGN and B2101J are all single-arm clinical trials.
Abbreviations: GRACE: Good Research for Comparative Effectiveness; N/A: not applicable.
Source: ELIANA CSR (31st Dec 2017);[68] ENSIGN CSR (6th Oct 2017);[70] B2101J CSR (30th Jan 2017).[71]

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 Clinical effectiveness results overview

An overview of the clinical effectiveness results from all three trials is provided in Table 12 below.

Table 12: Summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J

n (%)	ELIANA (N=79)[a]	ENSIGN (N=64)	B2101J (N=57)[b]
Primary efficacy results			
BOR[c]			
ORR (CR+CRi) (95% CI; p value)	65 (82.3%) (72.1, 90.0; NR)	45 (70.3%) (57.6, 81.1; <0.0001*)	54 (94.7%) (85.4,98.9)
CR	49 (62.0%)	38 (59.4%)	42 (73.7%)
CRi	16 (20.3%)	7 (10.9%)	12 (21.1%)
NR	7 (8.9%)	13 (20.3%)	3 (5.3%)
Unknown[d]	7 (8.9%)	6 (9.4%)	0
ORR with bone marrow MRD negative (i.e. MRD <0.01%) (95% CI)	64 (81.0%) (70.6, 89.0)	43 (67.2%) (54.3, 78.4)	49 (86.0%) (74.2, 93.7)
n (%)	**ELIANA (N=79)**	**ENSIGN (N=64)**	**B2101J (N=57)[b]**
Secondary efficacy results			
DoR (/RFS)			
% event free at 6 months (95% CI)	80.8 (68.0, 88.9)	79.5 (62.9, 89.3)	73.6 (58.7, 83.8)
% event free at 12 months (95% CI)	67.4 (53.2, 78.1)	70.5 (52.8, 82.6)	61.0 (45.0, 73.6)
% event free at 60 months (95% CI)	49.2 (34.6, 62.3)	N/A	44.9 (29.4, 59.3)
Median (months) (95% CI)	46.8 (17.8, NE)	NE (13.6, NE)	27.9 (8.0, NE)
EFS			
% event free at 6 months (95% CI)	71.7 (59.8, 80.6)	67.0 (53.5, 77.4)	74.3 (60.4, 83.9)

% event free at 12 months (95% CI)	57.2 (44.5, 68.0)	53.6 (39.3, 66.0)	57.8 (42.4, 70.4)
% event free at 60 months (95% CI)	41.8 (29.1, 53.9)	N/A	42.5 (27.7, 56.6)
Median (months) (95% CI)	23.7 (9.2, NE)	15.6 (6.4, NE)	24.9 (8.6, NE)
OS			
% at 6 months (95% CI)	88.6 (79.3, 93.9)	84.4 (72.9, 91.3)	86.0 (73.9, 92.7)
% at 12 months (95% CI)	77.1 (66.1, 84.9)	65.4 (52.4, 75.7)	78.9 (65.9, 87.5)
% at 60 months (95% CI)	55.7 (43.6, 66.3)	N/A	46.5 (30.8, 60.8)
Median (months) (95% CI)	NE (45.6, NE)	29.9 (15.1, 42.4)	47.7 (28.3, NE)

[a]Primary endpoint analysis was not repeated in ELIANA CSR (17th Nov 2022);[2] data for ELIANA primary efficacy presented refer to interim analysis performed in the ELIANA CSR (13th Apr 2018)[63] and presented in Grupp *et al.* 2019.[72]
[b]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[c]BOR is reported within 3 months, 6 months and 28 days of tisagenlecleucel respectively for ELIANA, ENSIGN and B2101J, respectively.
[d]'Unknown' is assigned in case the Baseline assessment of the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame.
*No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: CR with incomplete blood count recovery; DOR: duration of remission; FAS: full analysis set; MRD: minimum residual disease; NE: not estimable; NR: not reported; ORR: overall remission rate
Source: ELIANA CSR (13th Apr 2018);[63] ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] Grupp *et al.* (2019);[72] Laetsch *et al.* (2023).[12]; Grupp *et al.* (2018).[73]

B.2.6.2 ELIANA

Data from the ELIANA trial are presented from the latest data cut-off date of 17th Nov 2022 (n=79) and final primary and key secondary endpoint analysis performed at the data cut-off of 13th Apr 2018 (n=79).[2, 63] Final primary (i.e. ORR) and key secondary endpoint analyses (i.e. bone marrow MRD status) were met in the final primary endpoint analysis (DCO 13th Apr 2018) and hence, not repeated in the long term follow-up analysis (DCO 17th Nov 2022).[2, 63] Details of the interim and final analyses performed for the ELIANA trial are summarised in Table 13.

Table 13: Summary of analyses performed for ELIANA

Date of Data Cut-off	17th Aug 2016 (N=50)	31st Dec 2017 (N=77)	13th Apr 2018 (N=79)	17th Nov 2022 (N=79)
Description of Analysis	First Interim Analysis	Second Interim Analysis	Final Primary Endpoint Analysis	Long Term Follow-up (LPLV)
Median duration of study follow-up from infusion to data cut-off	4.3 months	20.8 months	24.0 months	79.4 months
Endpoints analysed	ORR, bone marrow MRD status, DoR, RFS, EFS, OS, EQ-5D, PedsQL	ORR, bone marrow MRD status, DoR, RFS, EFS, OS, EQ-5D, PedsQL	**ORR, bone marrow MRD status**, DoR, RFS, EFS, OS, EQ-5D, PedsQL	**DoR, RFS, EFS, OS, EQ-5D, PedsQL**
Data presented in previous NICE submission (TA554)?[1]	**Yes**	**Yes**	**Yes**	**No**

Endpoints in bold are presented in this submission. Details on the outcomes of the interim analyses performed can be found in NICE TA554.[1]

Abbreviations: DoR: duration of remission; EFS: event-free survival; EQ-5D: European quality of life 5 dimensions; MRD: minimal-residual disease; ORR: overall remission rate; OS: overall survival; PedsQL: pediatric quality of life; RFS: relapse-free survival.
Source: ELIANA CSR (17th Aug 2016);[74] ELIANA CSR (31st Dec 2017);[68] ELIANA CSR (13th Apr 2018);[63] ELIANA CSR (17th Nov 2022);[2] NICE TA554;[1] Grupp *et al.* (2019).[72]

Primary outcome: ORR

ELIANA met its primary endpoint with an ORR of 82.3% (95% CI: 72.1, 90.0)[12]

The primary outcome of the ELIANA trial was ORR within 3 months of tisagenlecleucel administration as determined by IRC assessment; the primary endpoint was an ORR of >20% (the alternative hypothesis). ORR was defined as the proportion of patients with a best overall disease response of CR or CRi on the basis of the results of laboratory testing of blood, bone marrow, and cerebrospinal fluid (CSF), as well as physical examination. Responses were required to be maintained for 28 days.[67]

ELIANA met its primary endpoint during the first interim analysis performed on 16th Dec 2016 with a data cut-off date of 17th Aug 2016. Subsequent interim analyses performed have been summarised in Table 13 above and further details on the outcomes of these analyses performed can be found in NICE TA554.[1] As of the final primary endpoint analysis (data cut-off of 13th Apr 2018), the ORR in the full analysis set was 82.3% (65/79) (95% CI: 72.1, 90.0), consistent with results from previous interim analyses.[12] In patients achieving ORR, CR was achieved in 49 patients (75.4%) and 16 patients (24.6%) achieved a CRi.[72]

There was one case of discrepancy between IRC assessment and the local Investigator assessment with regards to BOR. CR is a demonstrated surrogate outcome for survival benefit in patients with leukaemia.[75, 76] Compared to patients who have not achieved CR, patients who have achieved CR are associated with longer progression-fee survival and improvement in quality of life.[77] As outlined in Section B.1.3.2, the only curative approach to the treatment of relapsed B-cell ALL is allo-SCT; achieving CR is a prerequisite for allo-SCT, and thus achievement of CR is a critically important outcome for patients with r/r B-cell ALL.[34] Similarly, ORR and MRD-negative are standard outcome measures in ALL due to their correlation with long-term clinical outcomes.[78] Full results of the ORR analyses in the full analysis set are summarised in Table 14.

Table 14: Summary of IRC-assessed ORR within three months post-tisagenlecleucel infusion in ELIANA (full analysis set)

	Final Primary Analysis: 13th Apr 2018 (full analysis set) (N=79)[a]
BOR, n (%)	
CR	49 (62.0)
CRi	16 (20.3)
NR/unknown[b]	14 (17.7)
ORR (CR + CRi), n (%) (95% CI; p value)	65 (82.3) (72.1, 90.0; NR)

[a]Data presented refer to final primary analysis performed in the ELIANA CSR (13th Apr 2018)[63] and published in Grupp *et al.* (2019).[72]
[b]'Unknown' is assigned in case the Baseline assessment of the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; ORR: overall remission rate.
Source: Maude *et al.* (2018);[79] ELIANA CSR (13th Apr 2018);[63] ELIANA CSR (17th Nov 2022);[2] Grupp *et al.* (2019).[72]

Bone marrow MRD status

Of patients who achieved an ORR of CR or CRi, 98.5% had MRD negative disease, a key prognostic factor and marker of deep remission[73]

Bone marrow MRD status by IRC assessment during the 3 months post-tisagenlecleucel infusion as determined by IRC assessment was a key secondary endpoint outcome of the ELIANA trial. Bone marrow MRD status was assessed by flow cytometry, and was defined as the minimum MRD percentage during the corresponding time frame. MRD status can be used to assess early treatment response and to detect relapse in a precise manner.[78] An MRD of less than 0.01% was defined as 'MRD negative disease'.[80]

ELIANA met all three key secondary endpoints: (1) ORR, (2) bone marrow MRD status in patients who received tisagenlecleucel from US manufacturing facilities and (3) in patients who received tisagenlecleucel from all manufacturing facilities.

As of the Final Primary Analysis (DCO 13th Apr 2018), 65 of the 79 patients infused with tisagenlecleucel (82.3%; 72.1, 90.0) achieved an ORR of CR or CRi during the three months post-tisagenlecleucel infusion, of which 64/65 (98.5%) of patients were bone marrow MRD negative (i.e. MRD <0.01%).[2, 12, 72, 73] This was consistent with the results from the first interim analysis performed on the first 50 patients of which 41/50 (82.0%; 68.6, 91.4; $p < 0.0001$) were bone marrow MRD negative.[2, 79]

Given the prognostic association with MRD status and its use as a robust indicator of relapse, the results for this key secondary outcome demonstrate the depth and quality of the response achieved by tisagenlecleucel as assessed by bone marrow MRD negative remission rate in patients with an ORR of CR/CRi.[68] Full results of the bone marrow MRD status analyses are summarised in Table 15.

Table 15: Summary of IRC-assessed bone marrow MRD status within three months post-tisagenlecleucel infusion in ELIANA (full analysis set)

	Final Primary Analysis data cut-off: 13th Apr 2018 (full analysis set) (N=79)[a]	
	n (%)	95% CI
Achieved BOR of CR or CRi within 3 months of tisagenlecleucel infusion	65 (82.3)	72.1, 90.0
With bone marrow MRD negative status (i.e. MRD% <0.01%), n (%) (CI; p-value)	64 (81.0)	70.6, 89.0

[a]ORR from the Final Primary Analysis April 2018 data-cut of ELIANA was assessed in patients with 3 months post-tisagenlecleucel infusion only.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; FAS: full analysis set; IRC: independent review committee; MRD: minimal residual disease.
Source: ELIANA CSR (17th Nov 2022);[2] Grupp *et al.* (2019).[72]

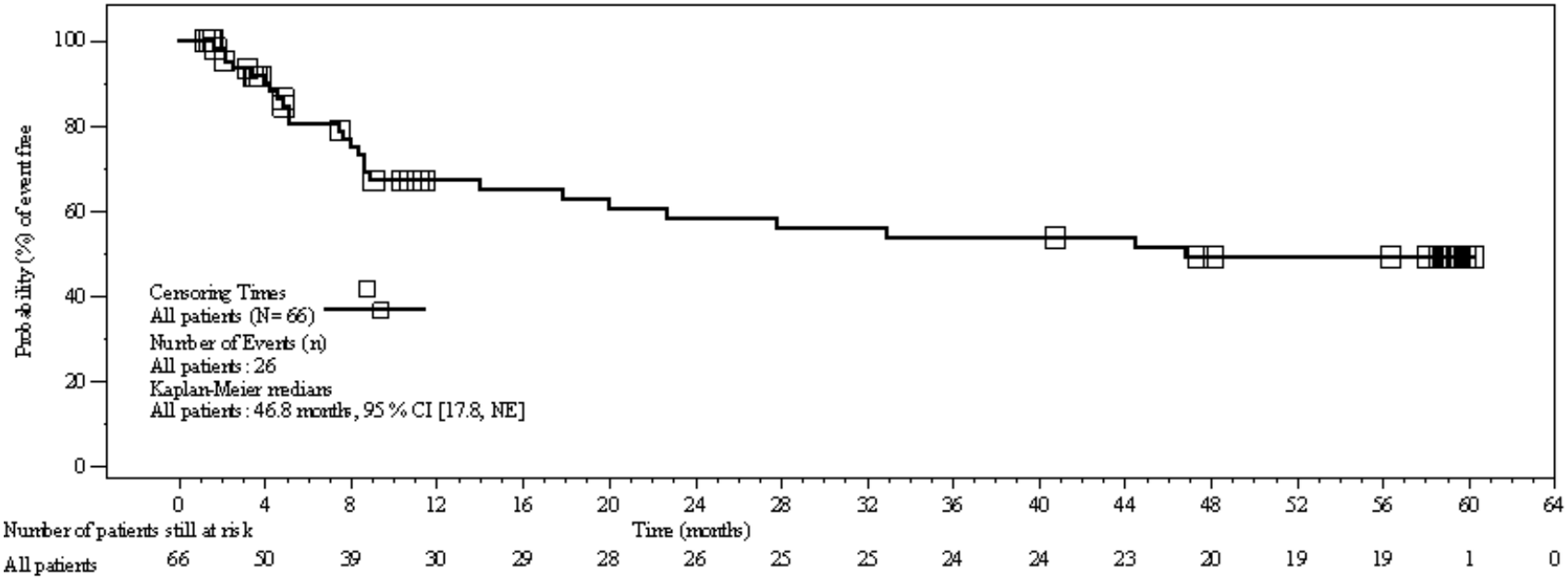
DoR

Remissions were durable; median DoR and RFS was 46.8 months and RFS rate at Month 60 was 49.2% (95% CI: 34.6, 62.3)[2]

DoR was defined as the time from the date of achievement of CR or CRi to the date of relapse or death due to underlying cancer, as determined by IRC assessment. RFS was defined as the time from achievement of CR or CRi whichever occurred first, to relapse or death due to any cause. As of the latest data cut-off date (17th Nov 2022), among patients with a BOR of CR or CRi, there were no deaths due to reasons other than the underlying cancer, and thus RFS was the same as DoR.[2]

As of the latest data cut-off date (17th Nov 2022), 39.4% (26/66) of patients who had achieved a BOR of CR or CRi reported relapse or death due to underlying cancer while median DoR was 46.8 months (95% CI: 17.8, NE).[2] The estimated rate of RFS after onset of remission was 80.8% (95% CI: 68.0, 88.9) at Month 6, 67.4% (95% CI: 53.2, 78.1%) at Month 12 and 49.2% (95% CI: 34.6, 62.3) at Month 60.[2, 12] The DoR per investigator assessment (censoring for HSCT and without censoring for HSCT) was similar to that determined by IRC assessment. DoR is considered as a useful outcome measure in oncology to assess the durability of treatment response and delay in disease progression.[81] The Kaplan–Meier plot for the analysis of DoR (DCO 17th Nov 2022) is presented in Figure 8. These results demonstrate the durability of responses achieved with tisagenlecleucel.

Figure 8: Kaplan–Meier plot for IRC-assessed DoR (censoring for allo-SCT) in ELIANA (full analysis set)



Abbreviations: CI: confidence interval; DoR: duration of remission; IRC: independent review committee; NE: not estimable.
Source: ELIANA CSR (17th Nov 2022).[2]

EFS

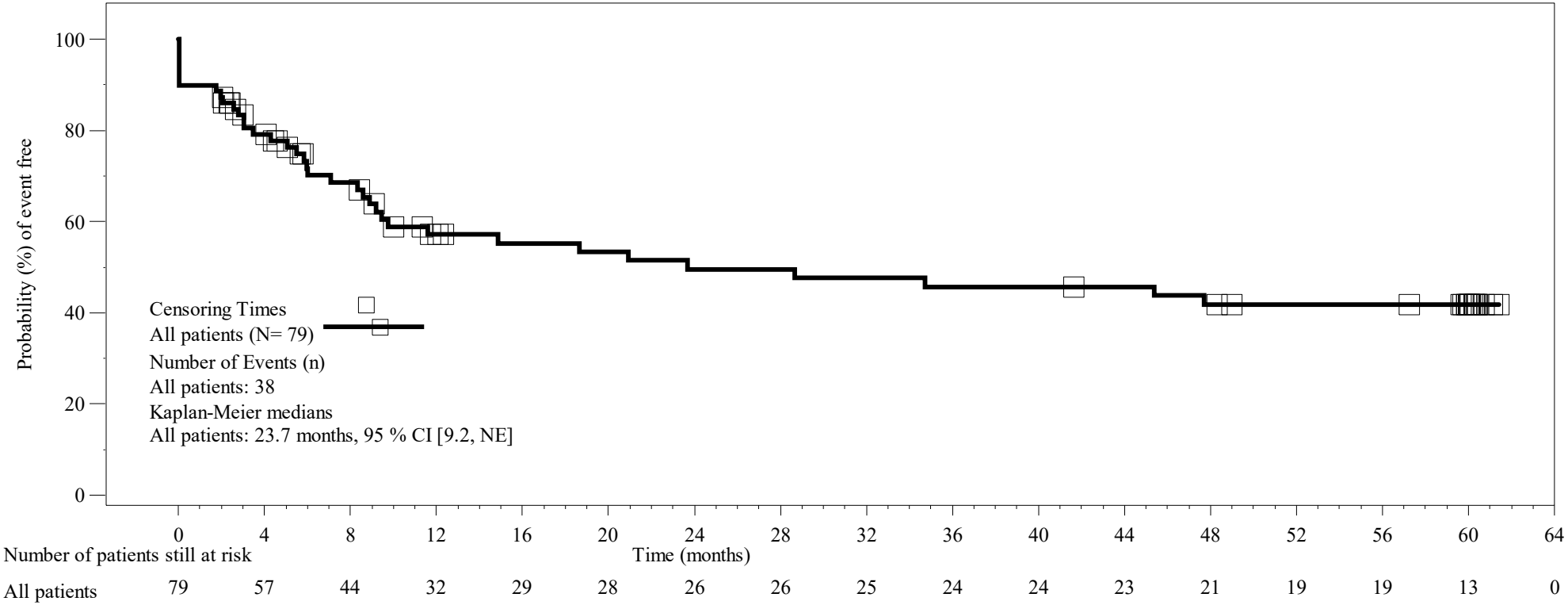
Median EFS was 23.7 months and EFS rate at Month 60 was 41.8% (95% CI: 29.1, 53.9)[2]

EFS was defined as the time from the date of first tisagenlecleucel infusion to the earliest date of either death due to any cause after remission, relapse, or treatment failure, as determined by IRC assessment. Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or new anticancer therapy. In case of treatment failure, the event date was set to study Day 1.[2]

At the time of the latest data cut-off (17th Nov 2022), median EFS was 23.7 months (95% CI: 9.2, NE) and only 38 of the 79 patients infused with tisagenlecleucel (48.1%) had experienced an EFS event (death due to any cause after remission, relapse, or treatment failure). The probability of being event-free was 71.7% (95% CI: 59.8, 80.6) at Month 6, 57.2% (95% CI: 44.5, 68.0) at Month 12 and 41.8% (95% CI: 29.1, 53.9) at Month 60.[12, 68]

The Kaplan–Meier plot for the analysis of EFS (data cut-off date of 17th Nov 2022) is presented in Figure 9, with a clear plateau emerging from approximately 24 months, demonstrating that treatment with tisagenlecleucel is associated with sustained, long-term EFS for a proportion of patients. As outlined in Section B.1.3.1, patients with ALL have poor prognosis that decreases with each subsequent relapse.[46] EFS is considered a surrogate endpoint for OS and can provide a direct assessment of the treatment benefit.[81] Given the association of progressed disease with poor HRQoL and medical and psychosocial consequences, prolonged EFS can also alleviate ALL disease burden for both patients and caregivers.[21, 30, 31] Achieving durable EFS is therefore an important outcome for treatment of r/r B-cell ALL.

Figure 9: Kaplan–Meier plot for IRC-assessed EFS (censoring for allo-SCT) in ELIANA (full analysis set)



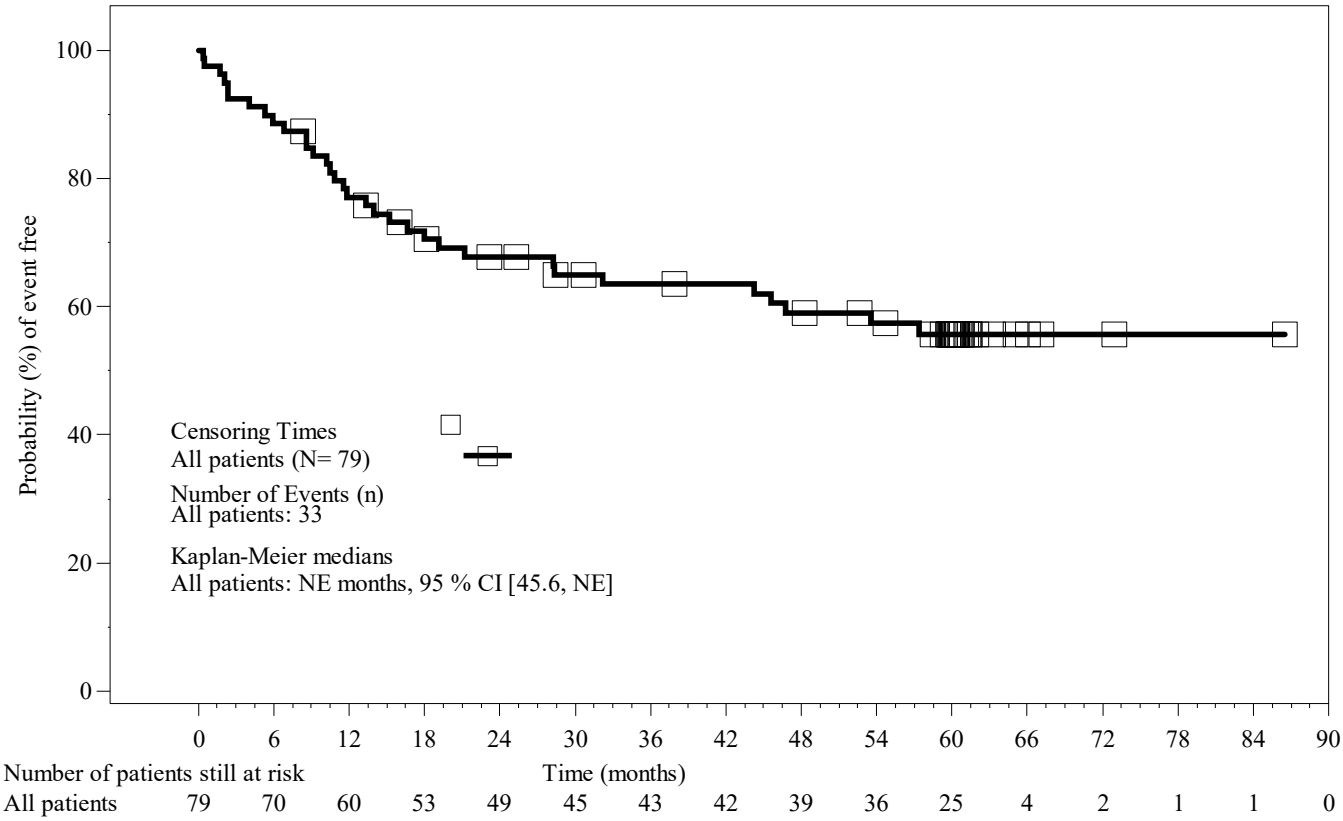
Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable.
Source: ELIANA CSR (17th Nov 2022).[2]

OS

OS data demonstrate durable remissions and a high probability of long-term survival; Median OS was not reached and OS rate at Month 60 was 55.7% (95% CI: 43.6, 66.3)[2]

OS was defined as the time from first tisagenlecleucel infusion to the date of death due to any cause.[2] At the time of the latest data cut-off (17th Nov 2022), median OS was not reached and without censoring for HSCT, 33/79 patients (41.8%) had died following tisagenlecleucel infusion. The probability of survival at Month 6 was 88.6% (95% CI: 79.3, 93.9), at Month 24 was 67.8% (95% CI: 56.1, 77.0) and at Month 60 was 55.7% (95% CI: 43.6, 66.3).[68] The Kaplan–Meier plot for the analysis of OS at the data cut-off date of 17th Nov 2022 is presented in Figure 10, with a clear plateau emerging from approximately 24 months, demonstrating that treatment with tisagenlecleucel is associated with durable remissions and prolonged OS for a proportion of patients.

Figure 10: Kaplan–Meier plot for OS in ELIANA (full analysis set)



Abbreviations: CI: confidence interval; OS: overall survival; NE: not estimable.
Source: ELIANA CSR (17th Nov 2022).[2]

Patient-reported outcomes

Patient-reported outcomes (PROs) were assessed via the paediatric quality of life questionnaire (PedsQL) and the EQ-5D questionnaire in patients ≥8 years old only.[82, 83]

The PedsQL is a generic instrument that is commonly used to measure HRQoL in children. The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults and in adolescents aged 12 to 18 years. A child-friendly version, the EQ-5D-Y, has been developed for use in children aged 8 years and older.[84] In the ELIANA trial, EQ-5D-3L was used for patients aged 13 and above at study entry and EQ-5D-Y was used for patients between the

ages of 8 and 12 years at study entry. Each patient completed the questionnaire(s) at each scheduled visit before interacting with the Investigator or undergoing other clinical assessments.

PedsQL questionnaire

For patients ≥8 years old who achieved CR/CRi following tisagenlecleucel infusion, higher mean scores on the PedsQL questionnaire for emotional, social, school, physical, and psychosocial health subscales were reported at Month 3, 6, 9, 12, 24 and 60 compared to Baseline, indicating consistent improvement of HRQoL over five year following tisagenlecleucel infusion. However, results beyond Month 12 should be interpreted with caution, as the number of patients with PRO results after this timepoint were limited (see Figure 11).[68]

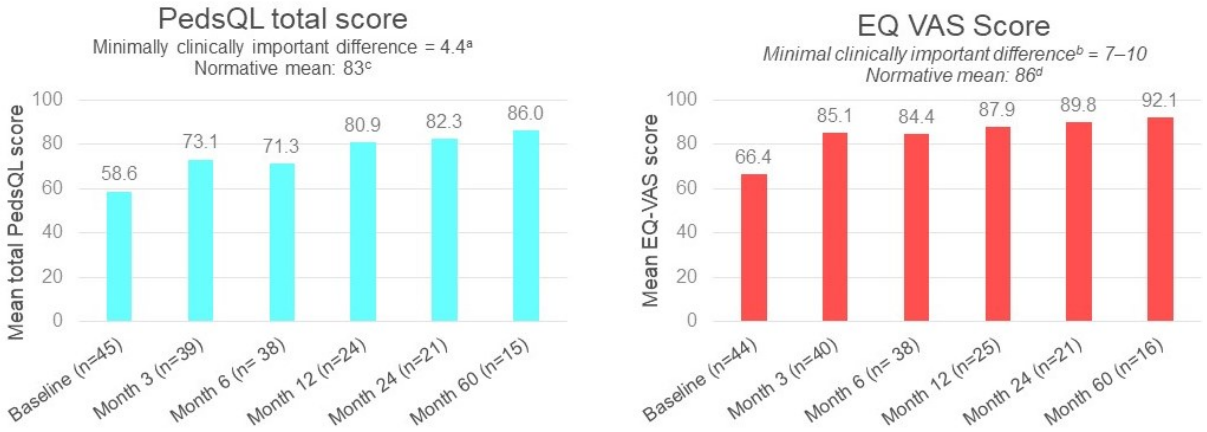
In the full analysis set (data cut-off 17th Nov 2022), the mean change from Baseline in the PedsQL total score was 14.8 at Month 6, 23.8 at Month 12, 26.2 at Month 24 and 25.3 at Month 60, indicating an overall improvement in HRQoL after tisagenlecleucel infusion.[2] The minimal clinically important difference for the PedsQL total scores has been estimated using distribution-based methods to be 4.4 for self-report.[85] Thus, the observed changes from Baseline in the PedsQL total score and in each PedsQL subscale at each time point represent clinically meaningful improvements in HRQoL.

EQ-5D-3L

For patients ≥8 years old who achieved CR/CRi following tisagenlecleucel infusion, the mean change from Baseline in the European quality of life visual analogue scale (EQ VAS) was 16.9 at Month 6, 20.5 at Month 12, 22.4 at Month 24, and 23.6 at Month 60, again indicating an overall improvement in HRQoL following tisagenlecleucel infusion (see Figure 11).[2] The number of patients is relatively small at the later timepoints and therefore interpretation should again be conducted with caution.

Given that minimally important differences for the EQ VAS among cancer patients were estimated to range from 7–10 using anchor-based categories from the Functional Assessment of Cancer Therapy - General (FACT-G) (Pickard *et al.* [2007]), the observed changes from Baseline in EQ VAS at each timepoint appear to represent meaningful improvements in HRQoL.[86] Additionally, while the mean EQ VAS score at Baseline (66.4) was comparable to that of patients sampled from cancers of various aetiologies (Pickard *et al.* [2007]), the mean scores at Month 6 (84.4), Month 12 (87.9), Month 24 (89.8), and Month 60 (92.1) were comparable to normative means of general populations.[2, 86, 87]

Figure 11: Summary of PedsQL and EQ VAS scores in ELIANA (patients ≥8 years old achieving CR/CRi)



Abbreviations: CR: complete remission; CRi: complete remission with incomplete blood count recovery; EQ VAS: EuroQol-visual analogue scales; HRQoL: health-related quality of life; PedsQL: Pediatric quality of life.
Source: [a]Varni *et al.* (2003);[85] [b]Pickard *et al.* (2007);[86] [c]Varni *et al.* (2001);[88] [d]Janssen *et al.* (2014);[87] ELIANA CSR (17th Nov 2022).[2]

B.2.6.3 ENSIGN

Data from the ENSIGN trial are presented from the latest data cut-off of 24th May 2019, which provides median follow-up of 31.7 months and a maximum follow-up duration of 56.0 months between the first tisagenlecleucel infusion and LPLV.[6] All outcomes are presented for the full analysis set (all patients who received infusion of tisagenlecleucel; n=64). The results of the primary and secondary efficacy endpoints in the latest analysis with a data cut-off date of 24th May 2019 was consistent with that reported in the previous two interim CSRs.

Primary outcome: ORR

The primary outcome of the ENSIGN trial was ORR within 6 months of tisagenlecleucel administration as determined by IRC assessment. ORR was defined as the proportion of patients with a best overall disease response of CR or CRi on the basis of the results of laboratory testing of blood, bone marrow, and cerebrospinal fluid (CSF), as well as physical examination. Responses were required to be maintained for 28 days.[6]

ENSIGN met its primary endpoint during its first interim analysis with a data cut-off date of 1st Feb 2016 with an ORR of 69.0% (20/29) (95% CI: 43.6, 88.1). As of the latest data cut-off date of 24th May 2019, the study met its primary endpoint with an ORR of 70.3% (45/64) (95% CI: 57.6, 81.1), consistent with the ORR of 69% reported in previous two interim CSRs.[70, 89] CR was achieved in 38 patients (59.4%) and seven patients (10.9%) achieved a CRi.[6] In sensitivity analyses performed using local Investigator assessment, there was 100% concordance between IRC assessment and local Investigator assessment of ORR.[70] Full results of the ORR analysis are summarised in Table 16.

Table 16: Summary of IRC-assessed ORR within six months post-tisagenlecleucel infusion in ENSIGN (efficacy analysis set)

	ENSIGN (efficacy analysis set) (N=64)
BOR, n (%)	
CR	38 (59.4)
CRi	7 (10.9)

No response	13 (20.3)
Unknown[a]	6 (9.4)
ORR (CR + CRi), n (%)(95% CI; p value)[b]	45 (70.3) (57.6, 81.1; <0.0001*)

[a]'Unknown' is assigned in case the Baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame.
[b]No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; ORR: overall remission rate.
Source: ENSIGN CSR (24th May 2019).[6]

Bone marrow MRD status

Bone marrow MRD status by IRC assessment during the six months post-tisagenlecleucel infusion was a key secondary outcome for patients who received tisagenlecleucel in the ENSIGN trial. MRD status was assessed by flow cytometry, and was defined as the minimum MRD percentage during the corresponding time frame. An MRD of less than 0.01% is defined as 'MRD negative disease'.[6]

As of the latest data cut-off date of 24th May 2019, 45/64 patients (70.3%; 95% CI: 57.6, 81.1) achieved an ORR of CR or CRi during the six months post-tisagenlecleucel infusion, of which 43 patients (67.2%; 95% CI: 54.3, 78.4) were bone marrow MRD negative (i.e. MRD <0.01%) and therefore achieved bone marrow MRD negative remission.[6] Secondary efficacy endpoint results (i.e. proportion of patients with BOR of CR/CRi with MRD negative bone marrow, DoR, EFS and OS) in the latest date cut-off of 24th May 2019 were consistent with that reported in the previous two interim CSRs.[70, 89] Full results of the bone marrow MRD status analysis within six months post-tisagenlecleucel infusion are summarised in Table 17.

Table 17: Summary of IRC-assessed bone marrow MRD status within six months post-tisagenlecleucel infusion in ENSIGN (efficacy analysis set)

	ENSIGN (efficacy analysis set) (N=64)	
	n (%)	**95% CI**
Achieved BOR of CR or CRi within 6 months	45 (70.3)	57.6, 81.1
With bone marrow MRD negative status (i.e. MRD% <0.01%)	43 (67.2)	54.3, 78.4

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; MRD: minimal residual disease.
Source: ENSIGN CSR (24th May 2019).[6]

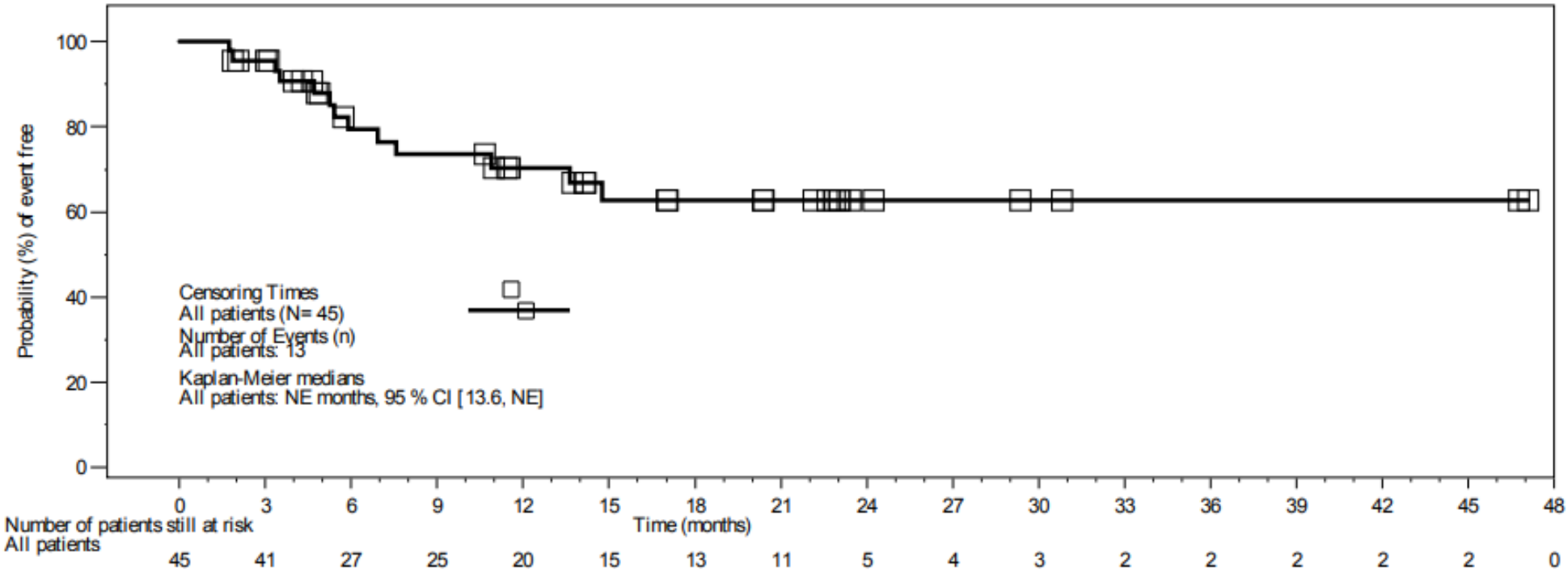
DoR

DoR was defined as the time from the date of achievement of CR or CRi to the date of relapse or death due to underlying cancer, as determined by IRC assessment. RFS was defined as the time from achievement of CR or CRi whichever occurred first, to relapse or death due to any cause. As of the latest data cut-off (24th May 2019), among patients with a BOR of CR or CRi, there were no deaths due to reasons other than the underlying cancer, and thus RFS was the same as DoR.[6]

As of the latest data cut-off (24th May 2019), 13/45 patients (28.9%) who achieved a BOR of CR or CRi had relapsed, while median DoR was 10.97 months. DoR prior to censoring for allo-SCT reported in the latest data cut-off analysis was similar to that reported in the second interim analysis. The estimated rate of RFS after onset of remission was 79.5% (95% CI: 62.9, 89.3) at Month 6, 70.5% (95% CI: 52.8, 82.6) at Month 12 and 62.8% (95% CI: 43.9, 76.9) at Month 30. A

pre-planned sensitivity analysis of DoR without censoring at time of allo-SCT was conducted in a previous data cut-off analysis (6th Oct 2017) and the results were similar to the main analysis (full results not shown).[70] The Kaplan–Meier plot for the analysis of DoR at the data cut-off date of 24th May 2019 is presented in Figure 12.

Figure 12: Kaplan–Meier plot for IRC-assessed DoR (censoring for allo-SCT) in ENSIGN (efficacy analysis set)



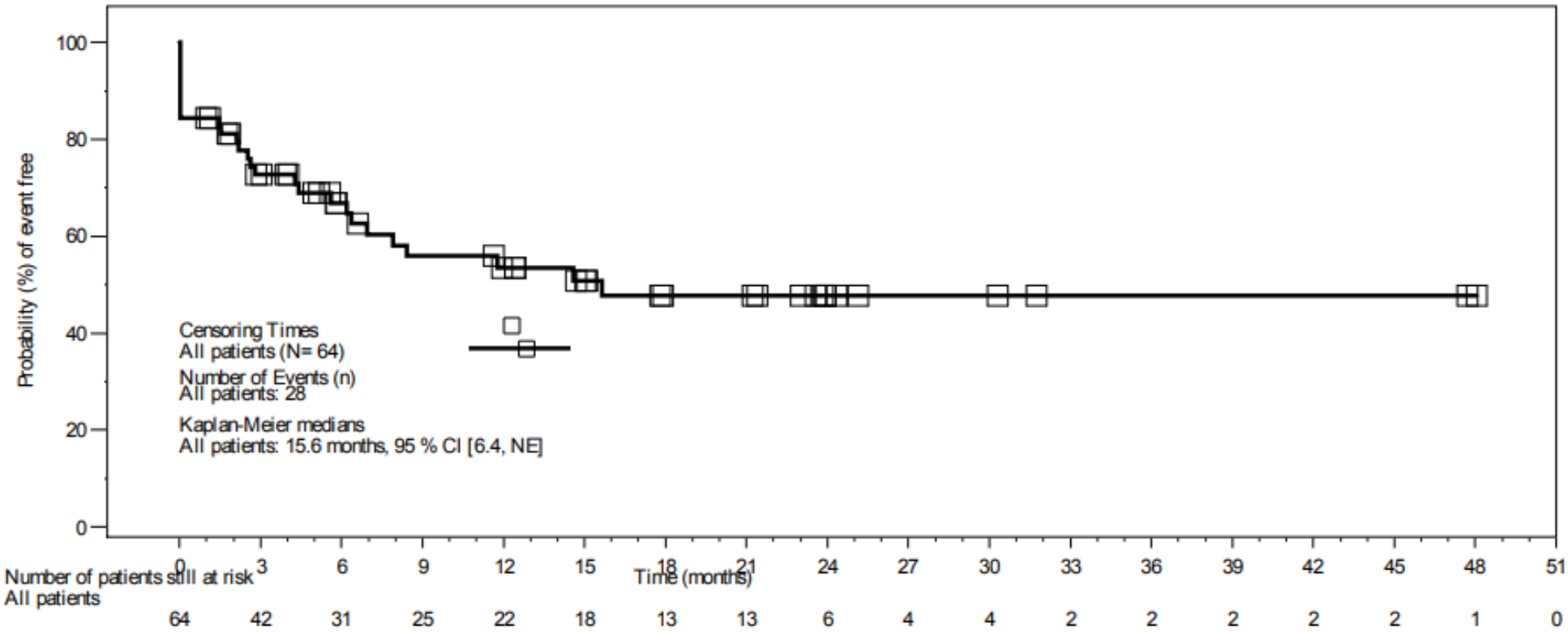
Time is relative to onset of remission, 1 month = 30.4375 days.
Abbreviations: CI: confidence interval; DoR: duration of response; IRC: independent review committee; NE: not estimable.
Source: ENSIGN CSR (24th May 2019).[6]

EFS

EFS was defined as the time from the date of first tisagenlecleucel infusion to the earliest date of either death due to any cause after remission, relapse, or treatment failure, as determined by IRC assessment. Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or new anticancer therapy. In case of treatment failure, the event date was set to study Day 1.[6]

At the time of the latest data cut-off (24th May 2019), median EFS was 15.6 months (95% CI: 6.4, NE) and 28 of the 64 patients (43.8%) reported treatment failure or relapse, as determined by IRC assessment.[6] The estimated probability of being event-free was 67.0% (95% CI: 53.5, 77.4) at Month 6, 53.6% (95% CI: 39.3, 66.0) at Month 12 and 47.8% (95% CI: 33.0, 61.1) at Month 30.[6] The Kaplan–Meier plot for the analysis of EFS at the data cut-off date of 24th May 2019 is presented in Figure 13, with a clear plateau emerging from approximately 15 months.

Figure 13: Kaplan–Meier plot for EFS (censoring for allo-SCT) in ENSIGN (full analysis set)

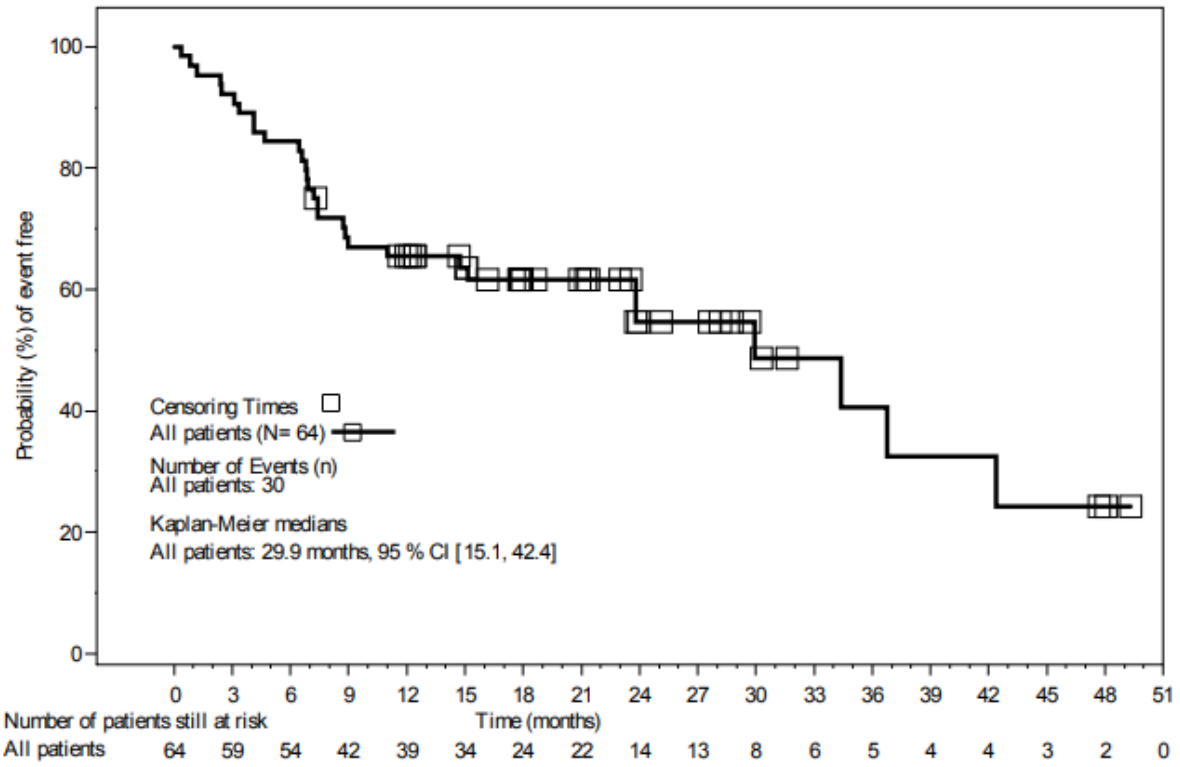


Time is relative to first tisagenlecleucel infusion date, 1 month = 30.4375 days. EFS of treatment failure patient is set to Day 1.
Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: ENSIGN CSR (24th May 2019).[6]

OS

OS was defined as the time from first tisagenlecleucel infusion to the date of death due to any cause. As of the latest data cut-off of 24th May 2019, median OS was 29.9 months (95% CI: 15.1, 42.4) and 30/64 patients (46.9%) had died following tisagenlecleucel infusion; however, the OS curve beyond 24 months should be interpreted with caution as only eight patients were at risk beyond that point.[6] The probability of survival at Month 6 was 84.4% (95% CI: 72.9, 91.3), and at Month 12 was 65.4% (95% CI: 52.4, 75.7).[6] The Kaplan–Meier plot for the analysis of OS at the data cut-off date of 24th May 2019 is presented in Figure 14.

Figure 14: Kaplan–Meier plot for OS in ENSIGN (full analysis set)



Time is relative to first tisagenlecleucel infusion date, 1 month = 30.4375 days.
Abbreviations: CI: confidence interval; OS: overall survival; NE: not estimable.
Source: ENSIGN CSR (24th May 2019).[6]

B.2.6.4 B2101J

Data from the B2101J trial are presented from the latest data cut-off date of 7th May 2018, which provides a median follow-up of 47.2 months and a maximum follow-up of 72.7 months following the first tisagenlecleucel infusion.[5] All outcomes are presented for the full analysis set (all patients who received infusion of tisagenlecleucel) in the 57 patients with non-CNS3 ALL only.

ORR

A key outcome of the B2101J trial was the ORR at Day 28 after tisagenlecleucel administration, as determined by Investigator assessment. ORR was defined as the proportion of patients with a best overall disease response of CR or CRi at the Day 28 visit. Disease assessment performed between study Day 2 to Day 59 and prior to the receipt of any new therapy was considered within the window.[5]

As of the latest data cut-off date of 7th May 2018, the ORR was 94.7% (54/57) (95% CI: 85.4, 98.9), with 16 patients (28.1%) achieving a CR and 38 patients (66.7%) achieving CRi by Day 28 post-tisagenlecleucel infusion. This was consistent with the ORR reported in previous interim analyses with an ORR of 94.6% (95% CI: 85.1, 98.9). In the analysis of BOR at any time for the latest data cut-off (7th May 2018), ORR was 94.7% (54/57) (95% CI: 85.4, 98.9), with 42 patients (73.7%) achieving CR and 12 patients (21.1%) with CRi. Only three patients (5.3%) did not respond to treatment with tisagenlecleucel.[5] Full results of the ORR analysis are summarised in Table 18.

Table 18: Summary of ORR at Day 28 in B2101J

	B2101J (full analysis set) (N=57)[a]
	n (%) (95% CI)
Overall response at Day 28	
CR	16 (28.1)
CRi	38 (66.7)
No response	3 (5.3)
Unknown	0 (0)
ORR: CR + CRi (at Day 28)	54 (94.7) (85.4, 98.9)
BOR at any time	
CR	42 (73.7)
CRi	12 (21.1)
No response	3 (5.3)
Unknown	0
ORR: CR + CRi (at any time)	54 (94.7) (85.4, 98.9)

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
Abbreviations: ALL: acute lymphoblastic leukaemia; BOR: best overall response; CI: confidence interval; CNS: central nervous system; CR: complete remission; CRi: complete remission with incomplete blood count recovery; MRD: minimal residual disease; ORR: overall remission rate.
Source: B2101J CSR (7th May 2018).[5]

Bone marrow MRD status

Bone marrow MRD status post-tisagenlecleucel infusion at Day 28, as determined by Investigator assessment, was a key secondary outcome for patients who received tisagenlecleucel in the B2101J trial. Bone marrow MRD status was assessed by flow cytometry, and was defined as the percentage of patients achieving MRD negative bone marrow post-tisagenlecleucel infusion; an MRD of less than 0.01% was defined as 'MRD negative disease'.[5]

As of the latest data cut-off of 7th May 2018, 54 of the 57 patients infused with tisagenlecleucel (94.7%; 95% CI: 85.4, 98.9) achieved a BOR of CR or CRi both at Day 28, or any time post-tisagenlecleucel infusion. At Day 28, negative bone marrow MRD status was achieved in 49 patients (86.0%), and at any time following infusion, 51 (89.5%) patients achieved bone marrow MRD negative remission.[5] Full results for the analysis of remission with MRD negative bone marrow are summarised in Table 19.

Table 19: Summary of bone marrow MRD status in B2101J (full analysis set)

	B2101J (full analysis set) (N=57)[a]	
	n (%)	95% CI
Achieved CR/CRi within 28 days	54 (94.7)	(85.4, 98.9)
With MRD negative disease status (i.e. MRD%<0.01%)	49 (86.0)	(74.2, 93.7)
Achieved CR/CRi at any time	54 (94.7)	(85.4, 98.9)
With MRD negative disease status (i.e. MRD%<0.01%)	51 (89.5)	(78.5, 96.0)

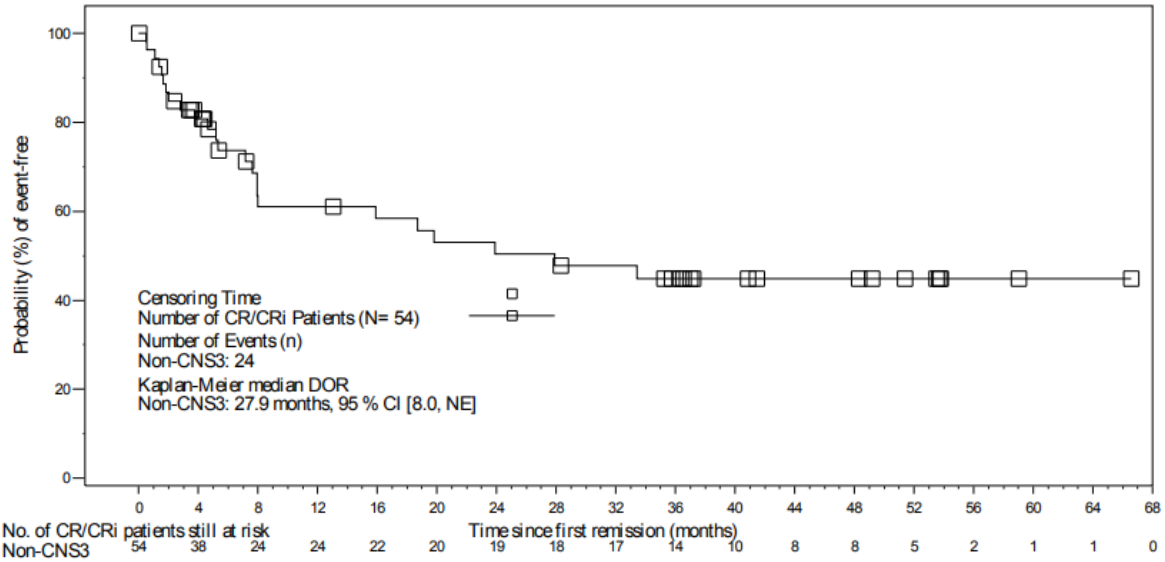
[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
Abbreviations: ALL: acute lymphoblastic leukaemia; CI: confidence interval; CNS: central nervous system; CR: complete remission; CRi: complete remission with incomplete blood count recovery; MRD: minimal residual disease.
Source: B2101J CSR (7th May 2018).[5]

DoR

DoR was defined as the duration from the date when the response criteria of CR or CRi was first met to the date of relapse or death due to underlying cancer. RFS was measured by the time from achievement of CR or CRi whichever occurred first, to relapse or death due to any cause during CR or CRi. RFS was assessed only in patients with a BOR of CR or CRi. As of the latest data cut-off (7th May 2018), among patients with a BOR of CR or CRi, there were no deaths due to reasons other than the underlying cancer, and thus RFS was the same as DoR.[5]

As of the latest data cut-off date (7th May 2018), 44.4% (24/54) of patients who achieved a BOR of CR or CRi had suffered an event (relapse or death due to underlying cancer), while the median DoR was 27.9 months. The estimated relapse-free rate after onset of remission was 61.0% (95% CI: 45.0, 73.6) at Month 12, 50.4% (95% CI: 34.5, 64.3) at Month 24, and remains constant at 44.9% (95% CI: 29.4, 59.3) from Month 36 onwards consistent with previously reported probabilities.[5] The Kaplan–Meier plot for the analysis of DoR at the data cut-off date of 7th May 2018 is presented in Figure 15.

Figure 15: Kaplan–Meier plot for DoR in B2101J (full analysis set)



Abbreviations: ALL: acute lymphoblastic leukaemia; CI: confidence interval; CNS: central nervous system; CR: complete remission; CRi: complete remission with incomplete blood count recovery; DoR: duration of response; NE: not estimable.
Source: B2101J CSR (7th May 2018).[5]

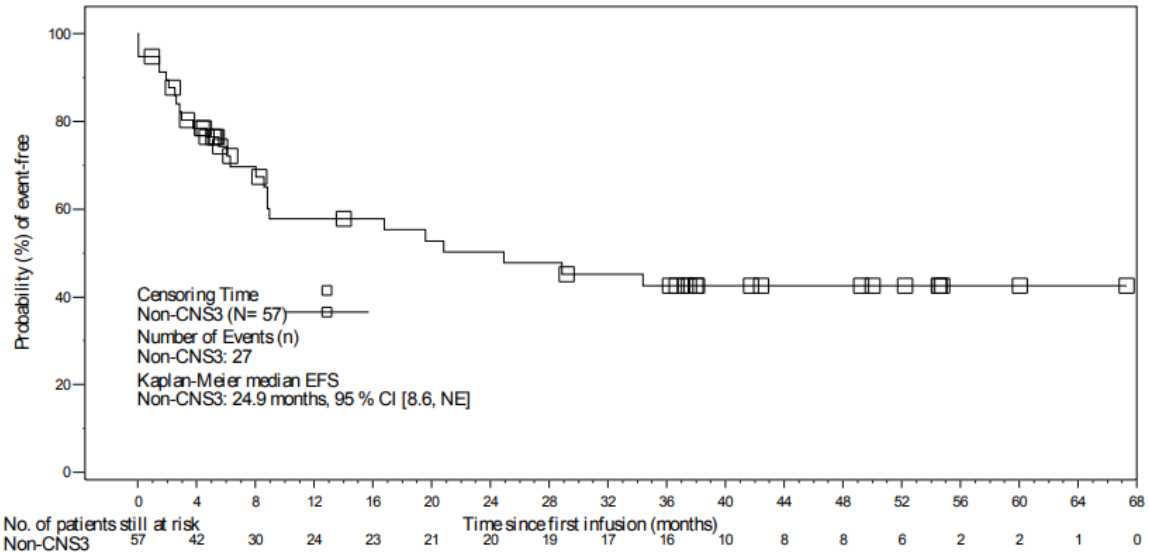
EFS

EFS was defined as the time from date of first tisagenlecleucel infusion to the earliest date of death due to any cause after remission, relapse, or treatment failure. Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or new anticancer therapy. In case of treatment failure, the event date was set to study Day 1.[5]

As of the latest data cut-off date (7th May 2018), median EFS was 24.9 months (95% CI: 8.6, NE), and 27/57 patients (47.4%) had experienced an event. The estimated probability of being event-free was 57.8% (95% CI: 42.4, 70.4) at Month 12, 50.2% (95% CI: 34.9, 63.7) at Month 24 and remains constant at 42.5% (95% CI: 27.7, 56.6) from Month 36 onwards.[5]

The Kaplan–Meier plot for the analysis of EFS at the data cut-off date of 7th May 2018 is presented in Figure 16, with a clear plateau emerging from approximately 28 months.

Figure 16: Kaplan–Meier plot for EFS in B2101J (full analysis set)

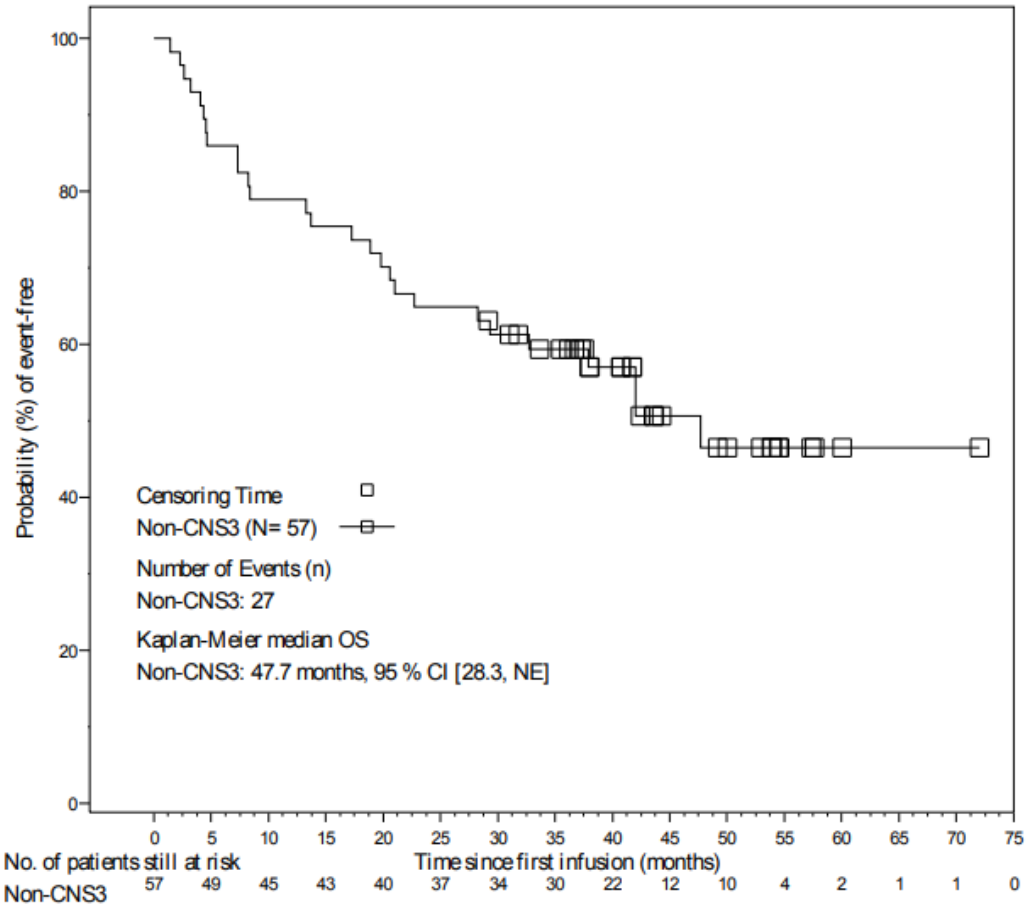


Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: B2101J CSR (7th May 2018).[5]

OS

OS was defined as the time from date of randomisation or first tisagenlecleucel infusion to the date of death due to any cause. As of the latest data cut-off of 7th May 2018, median OS was 47.7 months (95% CI: 28.3, NE) and 27/57 patients (47.4%) had died following tisagenlecleucel infusion. Compared to the previous data cut-off, five additional non-CNS3 ALL patients had died. The probability of survival was 78.9% (95% CI: 65.9, 87.5) at Month 12, 64.9% (95% CI: 51.1, 75.7) at Month 24, 59.4% (95% CI: 45.5, 70.9) at Month 36, and 46.5% (95% CI: 30.8, 60.8) at Month 60, demonstrating durable remission and a high probability of survival up to five years post-tisagenlecleucel infusion.[62] The Kaplan–Meier plot for the analysis of OS at the data cut-off date of 7th May 2018 is presented in Figure 17.

Figure 17: Kaplan–Meier plot for OS in B2101J (full analysis set)



Abbreviations: ALL: acute lymphoblastic leukaemia; CI: confidence interval; CNS: central nervous system; FAS: full analysis set; OS: overall survival; NE: not estimable.
Source: B2101J CSR (7th May 2018).[5]

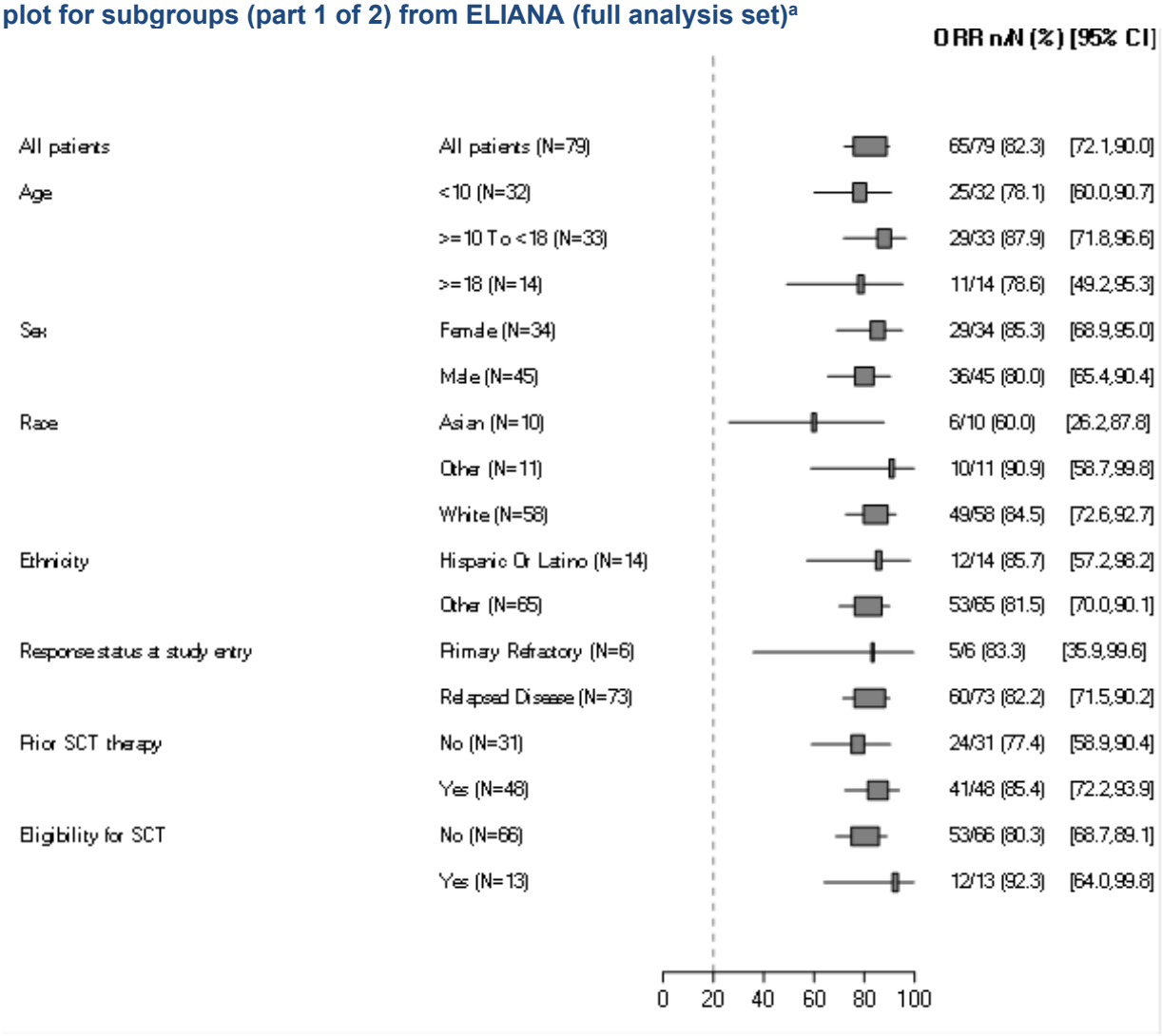
B.2.7 *Subgroup analysis*

In all three trials, the robustness and consistency of the primary analysis was confirmed by a series of pre-specified subgroup analyses for the ORR based on pre-determined baseline variables, including age, gender, baseline bone marrow tumour burden (an indicator of overall disease burden) and prior allo-SCT.

In the ELIANA trial, subgroup ORR analyses were conducted for subgroups with at least 5 patients for the data cut-off of 13th Apr 2018 (subgroup analyses were not performed for the latest data cut-off of 17th Nov 2022).[2] The ORR by IRC assessment was consistently ≥60% across all subgroups evaluated (hence the null hypothesis that the ORR was ≤20% could be rejected; see Figure 18 and Figure 19).

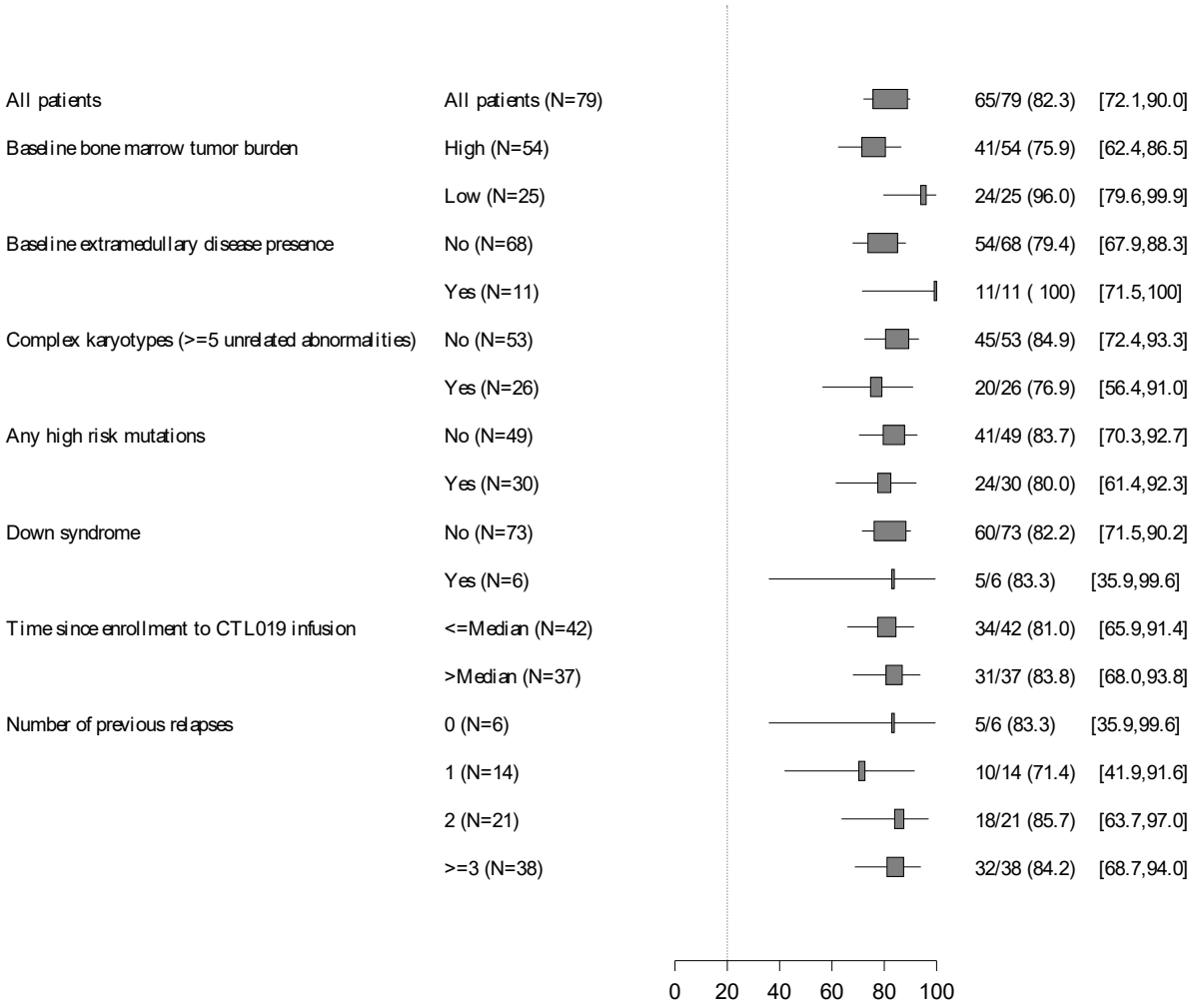
In the ENSIGN trial, subgroup ORR analyses by age were conducted for the data cut off of 24th May 2019, in which the ORR by IRC assessment across the various subgroups (with at least 10 patients) was consistently ≥60% (ranging from 60.0% to 73.5%). In B2101J (data cut-off 7th May 2018), the ORR by IRC assessment at Day 28 was similarly high in all pre-specified subgroups analysed (≥80% in all subgroups).

Figure 18: ORR within 3 months post-tisagenlecleucel infusion by IRC assessment. Forest plot for subgroups (part 1 of 2) from ELIANA (full analysis set)[a]



The area of each box is proportional to the number of patients in the particular grouping. 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.
[a]Data cut-off of 13th Apr 2018
Abbreviations: CI: confidence interval; IRC: independent review committee; ORR: overall remission rate; allo-SCT: stem cell transplantation.
Source: ELIANA CSR (13th Apr 2018).[63]

Figure 19: ORR within 3 months post-tisagenlecleucel infusion by IRC assessment. Forest plot for subgroups (part 2 of 2) from ELIANA (full analysis set)[a]



The area of each box is proportional to the number of patients in the particular grouping. 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.
[a]Data cut-off of 13th Apr 2018
Abbreviations: CI: confidence interval; IRC: independent review committee; ORR: overall remission rate; allo-SCT: stem cell transplantation.
Source: ELIANA CSR (13th Apr 2018).[63]

B.2.8 *Meta-analysis*

For the purposes of increasing the overall available sample size for tisagenlecleucel, data for EFS and OS from all three tisagenlecleucel clinical trials were pooled as part of a meta-analysis. The feasibility of pooling all three trials was assessed by taking into consideration the study design, definitions of outcomes, and patient baseline characteristics of all three tisagenlecleucel clinical trials and further details are presented in Appendix D.

Study design

All three trials followed almost identical study designs. The only difference for B2101J was the dosing regimen: in ELIANA and ENSIGN, patients received a single infusion with a narrower target dose range whereas in the B2101J study, patients were treated according to a dose escalation protocol, with a wider target dose range, and could therefore receive multiple infusions.[2, 5, 6] Whilst

this difference in dosing between the trials is noted, the median dose received across all three trials was of the same magnitude and therefore this difference was not expected to bias the pooled estimate of efficacy for tisagenlecleucel.

Outcome definitions

The definitions of EFS and OS, the key outcome measures informing the economic analysis, were identical across all three trials (see Table 6).

Patient baseline characteristics

The eligibility criteria of the B2101J trial were broader, and allowed the inclusion of patients with prior anti-CD19 therapy, CNS3 disease, and patients up to the age of 24 at diagnosis (compared with 21 years in ELIANA and ENSIGN).[5] However, only 4 patients in the B2101J trial had received prior anti-CD19 therapy and therefore this minority is not expected to have a large impact on the results of the trial. Furthermore, the analyses of the B2101J trial presented in this submission are for patients without CNS3 disease, hence this difference can be considered accounted for. In terms of age, the mean age across all three trials was very similar (12.04, 12.36 and 11.65 in ELIANA, ENSIGN, and B2101J, respectively) and the age range across all three trials was between 1 and 25.[2, 5, 6]

Key patient baseline characteristics can be found in Table 20 below. Overall, it was considered that any differences between baseline characteristics were minor, and therefore it was considered appropriate to pool the data from all three trials. Furthermore, the eligibility criteria of all three trials match the intended patient population for tisagenlecleucel in UK clinical practice.[2, 5, 6] Therefore, taken together, the pooling of all three trials generates a larger sample size of a group of patients that can be considered, overall, to be representative of the "true" population likely to be treated with tisagenlecleucel in UK clinical practice.

Table 20: Key patient baseline characteristics from the pooled analysis

	ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)[a]	Pooled (N=200)
Sex, n (%)				
Female	34 (43.0)	34 (53.1)	25 (43.9)	93 (46.5)
Male	45 (57.0)	30 (46.9)	32 (56.1)	107 (53.5)
Age				
Mean	12.04	12.36	11.65	12.03
Median	11.00	12.50	11.00	12.00
Min	3.00	3.00	1.00	1.00
Max	24.00	25.00	24.00	25.00
Trisomy, n (%)				
Yes	6 (7.6)	4 (6.3)	-	10 (5.0)
No	73 (92.4)	60 (93.8)	-	133 (66.5)
Missing	-	-	57 (100)	57 (28.5)
Previous remission				
Mean	2.35	1.88	2.07	2.12
Median	2.00	2.00	2.00	2.00

Min	0.00	0.00	0.00	0.00
Max	6.00	7.00	6.00	7.00
Prior HSCT, n (%)				
Yes	48 (60.8)	28 (43.8)	37 (64.9)	113 (56.5)
No	31 (39.2)	36 (46.2)	20 (35.1)	87 (43.5)
Previous lines of therapy				
Mean	3.46	2.92	4.26	3.52
Median	3.00	3.00	4.00	3.00
Min	1.00	1.00	1.00	1.00
Max	8.00	9.00	8.00	9.00
MLL total, n (%)				
Yes	1 (1.3)	3 (4.7)	1 (1.8)	5 (2.5)
No	78 (98.7)	61 (95.3)	56 (98.2)	195 (97.5)
BCR-ABL, n (%)				
Yes	2 (2.5)	2 (3.1)	3 (5.3)	7 (3.5)
No	77 (97.5)	62 (96.9)	23 (40.4)	162 (81.0)
Missing	-	-	31 (54.4)	31 (15.5)
Hypodiploidy, n (%)				
Yes	1 (1.3)	1 (1.6)	-	2 (1.0)
No	78 (98.7)	63 (98.4)	24 (42.1)	165 (82.5)
Missing	-	-	33 (57.9)	33 (16.5)
Months since previous relapse				
Mean	4.25	3.12	5.77	4.35
Median	3.50	2.60	5.10	3.65
Min	1.50	1.30	1.30	1.30
Max	13.8	9.8	20.50	20.50
Bone marrow blast count, n (%)				
>50% (high)	54 (68.4)	44 (68.8)	23 (40.4)	121 (60.5)
≤50% (low)	25 (31.6)	20 (31.3)	34 (59.6)	79 (39.5)

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b]For B2101J, this value refers to patients who have received >1 prior allo-SCT.
Abbreviations: BCR-ABL: breakpoint cluster region-Abelson; HSCT: haematopoietic stem cell transplant; MLL: mixed-lineage leukaemia.
Source: ELIANA CSR (31st Dec 2017);[68] ENSIGN CSR (6th Oct 2017);[70] B2101J CSR (30th Jan 2017);[71] Laetsch *et al.* (2022).[12]

The individual patient-level data (IPD) from each of the latest data cut-offs for all three clinical trials ELIANA (n=79), ENSIGN (n=64) and B2101J (n=57) were combined directly without adjustment to derive a pooled estimate of EFS and OS for tisagenlecleucel.[2, 5, 6] A total of 200 patients were therefore included in the pooled population.

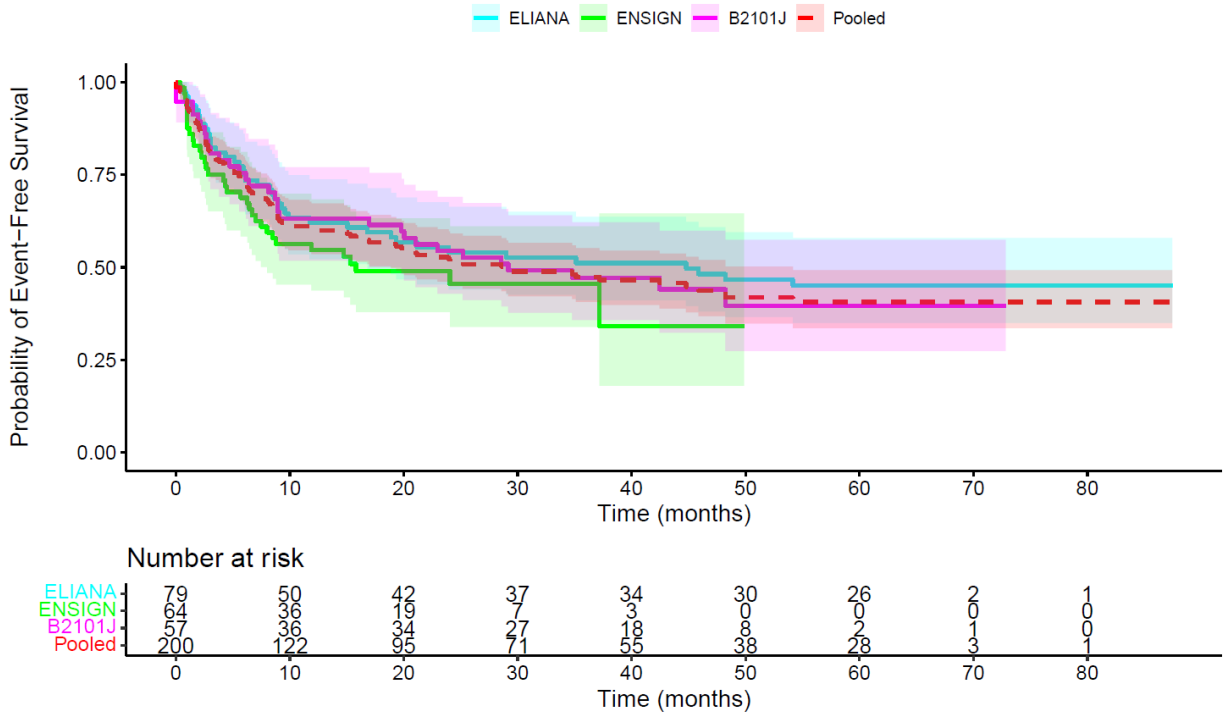
EFS

EFS was defined as the time from the date of first tisagenlecleucel infusion to the earliest date of either death due to any cause after remission, relapse, or treatment failure, as determined by IRC assessment. Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or new anticancer therapy. In case of treatment failure, the event date was set to study Day 1.[80]

In the pooled analysis, median EFS is 29.0 months (95% CI: 18.9, 54.2) and 108 of the 200 patients infused with tisagenlecleucel (54.0%) had experienced an EFS event (death due to any cause after remission, relapse, or treatment failure). The probability of being event-free was 60.0% (95% CI: 53.6%, 67.2%) at one year, 51.5% (95% CI: 44.9%, 59.1%) at two years, 47.3% at (95% CI: 40.6%, 55.2%) at three years, 41.8% (95% CI: 34.8%, 50.2%) at four years and 40.6% (95% CI: 33.6%, 49.2%) at five years.[2]

The Kaplan–Meier plot showing the EFS curve for each trial separately, together with the pooled EFS curve is presented in Figure 20 below.

Figure 20: Kaplan–Meier curves for EFS in ELIANA, ENSIGN and B2101J and the pooled population



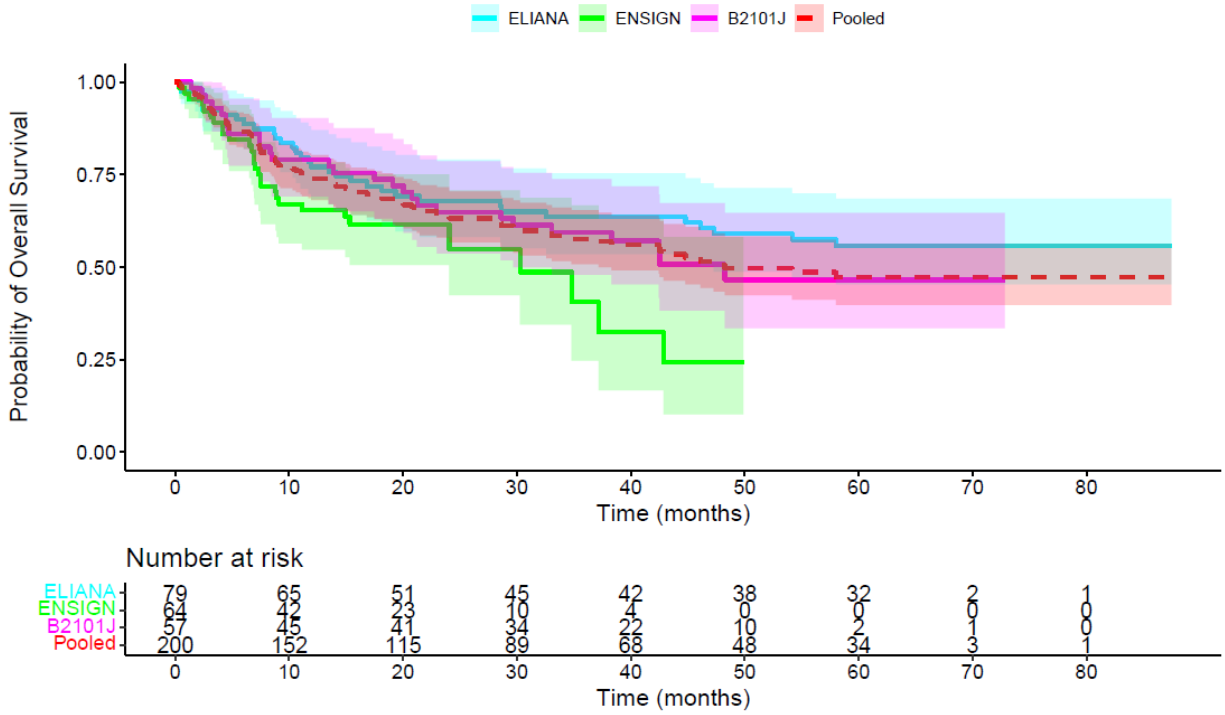
Abbreviations: EFS: event-free survival.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

OS

OS was defined as the time from first tisagenlecleucel infusion to the date of death due to any cause.[80] In the pooled analysis, median OS is 48.2 months (95% CI: 37.2, NA) and 90 of the 200 patients (45%) had died following tisagenlecleucel infusion. The probability of survival at one year was 73.9% (95% CI: 68.1%, 80.3%), 63.2% (95% CI: 56.6%, 70.4%) at two years, 57.6% (95% CI: 50.8%, 65.4%) at three years, 49.7% (95% CI: 42.4%, 58.3%) at four years and 47.3% (95% CI: 39.8%, 56.3%) at five years, indicating durable remission and a high probability of survival up to 5 years after infusion.[2]

The Kaplan–Meier plot showing the OS curve for each trial separately, together with the pooled OS curve is presented in Figure 21 below.

Figure 21: Kaplan–Meier curves for OS in ELIANA, ENSIGN and B2101J and the pooled population



Abbreviations: OS: overall survival.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

B.2.9 *Indirect and mixed treatment comparisons*

In the absence of head-to-head clinical trial evidence of tisagenlecleucel versus either blinatumomab or salvage chemotherapy (FLAG-IDA), an SLR was conducted to identify relevant evidence on the comparator treatments for the purposes of conducting a possible indirect treatment comparison. Full details of the methodology and results of the SLR are presented in Appendix D.

Blinatumomab

Of the 79 records from the 38 unique studies ultimately identified in the March 2023 SLR update, eight publications reporting on six studies were identified that investigated the use of blinatumomab in paediatric patients aged up to 18 years with r/r B-cell ALL. Of the included studies, a total of two studies that investigated the use of blinatumomab were prioritised for extraction and quality assessments as they were deemed potentially relevant to the indirect treatment comparisons and economic modelling.

This included a phase I/II open-label, multicentre, non-randomised study (n=70) published by Gore *et al.* (2018) and a single-arm expanded open-access study (n=110) published by Locatelli *et al.* (2022).[90, 91] The Locatelli *et al.* (2022) study is an extension of the RIALTO study which was previously identified in the original SLR conducted in March 2018 as part of the original submission (TA554).[91] A phase II clinical trial published by von Stackelberg *et al.* (2016) had also been identified in the original SLR and assessed alongside the RIALTO study on the suitability of the

two studies as comparator efficacy data sources.[7] A brief re-cap of the assessment performed in TA554 is as follows: The eligibility criteria of the RIALTO study permitted patients previously treated with blinatumomab, and therefore it was considered that some patients may have overlapped between the von Stackelberg *et al.* (2016) and RIALTO studies. For this reason, the RIALTO study had not been considered further in TA554 for inclusion within an indirect treatment comparison, nor was it considered appropriate to explore a pooling of the von Stackelberg *et al.* (2016) and RIALTO studies.[7] Being an extension of the RIALTO study, the Locatelli *et al.* (2022) study was hence not considered further for inclusion in the current submission.[91]

The Gore *et al.* (2018) study reports on the same pivotal clinical trial as that reported by von Stackelberg *et al.* (2016), but data are only reported by allo-SCT use before or after blinatumomab and thus are not comparable to the full tisagenlecleucel trial populations.[7, 90] As such, and given the von Stackelberg *et al.* (2016) study represents the pivotal clinical trial for blinatumomab in paediatric patients with r/r B-cell ALL and the lack of identification of new compelling data, the von Stackelberg *et al.* (2016) study alone was considered for further inclusion within an indirect treatment comparison, noting its acceptance by the committee in the original appraisal (TA554).[7, 9] Further details of the von Stackelberg *et al.* (2016) study are presented in Appendix D.[7]

Salvage chemotherapy (FLAG-IDA)

No trials were identified for FLAG-IDA in paediatric patients with r/r B-cell ALL in the March 2023 SLR update. Three studies were identified in the previous SLR update performed in July 2019 and were hence, assessed on their suitability as comparator efficacy data sources. This included a single-arm, open label phase IV study (n=28) published by Zwaan *et al.* (2017), a prospective cohort study in Italy (n=37) published by Bertaina *et al.* (2017) and a prospective cohort study in Austria (n=242) published by Kuhlen *et al.* (2018).[92-94] Details on these studies are summarised in Table 21.[92-94]

The studies published by Zwaan *et al.* (2017) and Bertaina *et al.* (2017) had small sample sizes and used chemotherapy regimens which were not considered as reasonable proxies for FLAG-IDA (i.e. nelarabine and a combination therapy of bortezomib and chemotherapy respectively).[92, 93] Hence, these studies were not considered as suitable comparator data sources for inclusion.[92, 93] The Kuhlen *et al.* (2018) was previously identified by the ERG in the original appraisal (TA554) but given that all patients in the study had prior-SCT and the patient population included approximately 20% of patients with extramedullary relapse, the patient population in Kuhlen *et al.* (2018) was not considered comparable to that of the tisagenlecleucel trials.[9, 94] As such, the Jeha *et al.* (2006) study used as the comparator data source in the original submission (TA554) was deemed the most appropriate for inclusion in the indirect treatment comparison performed in the current submission. [8, 9]

A brief re-cap of the assessment performed for clofarabine to be used as proxy evidence for the efficacy of FLAG-IDA in the original submission (TA554) is provided below, noting that the Jeha *et al.* (2006) study was also used as part of the NICE mock appraisal.[8, 9]

Six publications reporting on six studies on chemotherapy were identified in the March 2018 SLR and no trials explicitly using FLAG-IDA had been identified. The identification of the six publications was based on the following elements: 1) comparable patient population to the three tisagenlecleucel clinical trials; 2) relevant EFS and OS measures reported in the form of Kaplan-Meier curves; 3) comparability to patient population in the UK; 4) exclusion of studies on blinatumomab.

These six trials, summarised in

Table 22, were presented for review by UK clinical experts, who advised on whether the efficacy outcomes could be considered comparable to the outcomes expected with FLAG-IDA. Feedback from UK clinical experts in the original submission (TA554) was that median OS with FLAG-IDA would be around 3 months. Median OS for all 6 trials ranged from 11 weeks to 9 months, and therefore the trials with median OS of 9 months were further excluded, given these survival outcomes did not align with the clinical expert feedback. Based on this, only 4 possible trials remained, which investigated the use of clofarabine combination therapy (Hijiya *et al.* [2011]; Miano *et al.* [2012]; Cooper *et al.* [2013]) or clofarabine monotherapy (Jeha *et al.* [2006]).[8, 95-97] Feedback from UK clinical experts was that efficacy with clofarabine monotherapy or clofarabine combination therapy could be considered appropriate for use as a proxy for the clinical efficacy of FLAG-IDA.[14] Given the fact that clofarabine monotherapy is licensed in the UK for paediatric/young adult patients who have received at least two prior regimens, and the data were also used as part of the NICE mock appraisal, the study by Jeha *et al.* (2006) was ultimately considered to be the most appropriate source of clinical data for the salvage chemotherapy (FLAG-IDA) comparator within this submission.[8] The other clofarabine studies (Hijiya *et al.* [2011]; Miano *et al.* [2012]) relate to combination therapy and were therefore excluded on this basis. [95, 96]

Table 21: Clinical evidence identified in July 2019 SLR update to be used as a proxy for the efficacy of FLAG-IDA

Author year	Study design	Number of ALL patients	Country	Patient population: age	Intervention	Patient population: line of relapse	Patient population: prior allo-SCT	Prior therapies	Mean OS
Zwaan *et al.* (2017)[93]	Single-arm, open label phase IV study	28 patients	Germany and the Netherlands	• Patients aged <21 years • Median age at study entry 11.5 (3 to 22)	Nelarabine alone	2nd or further relapse	10.7% patients (3/28) with prior allo-SCT	NR	6.5 months
Bertaina *et al.* (2017)[92]	Prospective cohort study	37 patients	Italy	• Patients aged ≤15 years at time of diagnosis and ≤21 years at time of treatment • Median age at study entry 6.7 (0.9-15)	Bortezomib + chemotherapy	Mixed (1st relapse, 40.50%, 15/37)	40.50% patients (15/37) with prior allo-SCT	• 56% patients had 1-2 prior lines of therapy • 43% patients had >2 prior lines of therapy	1.1 years
Kuhlen *et al.* (2018)[94]	Prospective cohort study	242 patients	Austria	• Patients aged ≤19 years • Median age at study entry 11.29 (2.25 to 18.75)	Nelarabine alone or nelarabine + cyclophosphamide + etoposide	Mixed (1st relapse, 29.30%, 71/242)	All patients had prior allo-SCT	NR	Similar to EFS reported (7.7 months)

Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem cell transplantation; EFS: event-free survival; FLAG-IDA: fludarabine, cytarabine, G-CSF, idarubicin; G-CSF: granulocyte colony-stimulating factor; OS: overall survival; SLR: systematic literature review.
Source: Zwaan *et al*. (2017);[93] Bertaina *et al.* (2017);[92] Kuhlen *et al.* (2018).[94]

Table 22: Clinical evidence identified in March 2018 SLR to be used as a proxy for the efficacy of FLAG-IDA

Author Year	Study design	Number of ALL patients	Country	Patient population: age	Intervention	Patient population: line of relapse	Patient population: prior allo-SCT	Prior therapies	Median OS
Miano *et al.* (2012)[96]	Prospective cohort study	24 patients	Italy	• Patients between 1–20 years of age • Median age at diagnosis 4.6 (0.2–16.6) • Median age at study entry 7.8 (1.3–19.6)	• Clofarabine + cyclophosphamide + etoposide	• 2nd or further relapse or refractory • 4 (16.7%), 9 (37.5%), 9 (37.5%) and 2 (8.3%) with 0, 1, 2 and 3 prior relapses, respectively	At least 3 months post-transplant 50% patients (ALL and AML combined) had received prior allo-SCT, two patients had received two prior allo-SCTs	1–4 prior lines of therapy 6 (25%), 14 (58.3%) and 4 (16.7%) with 1, 2 and 3 or 4 prior courses of treatment, respectively	~3 months
Hijiya *et al.* (2011)[95]	Single-arm clinical trial	25 patients	US	• Age at initial diagnosis 1–21 years • Median age at study entry 14 (1–21)	• Clofarabine + cyclophosphamide + etoposide	• 1st 2nd or 3rd relapse • 16% (primary refractory 8%), 56% and 28% with 1, 2 and 3 prior regimens, respectively	Protocol amended so patients with prior allo-SCT were excluded BUT 16% patients with prior allo-SCT	• ≤3 prior induction regimens • 1–3 (median=2) prior lines of therapy	11 weeks
Locatelli *et al.* (2009)[98]	Open-label, multicentre, non-randomised study	25 patients	Italy	• Age ≤15 at diagnosis • Patients between 1–21 years of age at treatment • Median age at initial diagnosis 8 (1–15) • Median age	• Clofarabine + cyclophosphamide + etoposide	• Refractory, or multiple BM relapsed ALL • 24%, 8%, 68% with 2nd, 3rd relapse and refractory disease at treatment, respectively	No more than one prior allo-SCT 29% patients with prior allo-SCT	• No more than 3 prior induction regimens for ALL patients • Number of prior lines of therapy NR • First-line protocol: AIEOP ALL 2000 (64%)	~9 months (B-cell patients only)

				at study entry 12.5 (4–21)				• AIEOP ALL 95 (24%) • DFCI ALL (12%)	
Cooper *et al.* (2013)[97]	Single-arm clinical trial	21 patients (8 given clofarabine at 40 mg/m^2 and 13 at 52 mg/m^2)	US/ Canada	• Included patients 1–21 years • Age at initial diagnosis 6.2 (0.27–21.8) years • Age at study entry 11.8 (1.2–25.7)	• Clofarabine + cytarabine	• 2nd/3rd relapse or refractory to re-induction therapy in first relapse • 86% in 2nd **or** 3rd relapse • 14% refractory	• Excluded ALL patients that received allo-SCT within 12 months of study entry • 3 patients with ALL who had received prior allo-SCT were enrolled prior to the amendment, and 2 patients with prior allo-SCT were enrolled after amendment • 29% patients with prior allo-SCT	Relapsed patients allowed to have no more than 3 prior induction regimens	~3 months
Messinger *et al.* (2012)[99]	Single-arm clinical trial	22 patients	US	• Age <21 at initial diagnosis • >1 year at study entry • Median age	• Bortezomib + VXLD	• 2nd or 3rd relapse • No refractory disease	18% patients with prior allo-SCT	Patients were eligible only after they failed 2 or 3 previous treatment regimens	~9 months

				at study entry 12 (1.3–22.3)				• 77% failed 2 regimes • 23% failed 3 regimes	
Jeha *et al.* (2006) [8]	Single-arm clinical trial	61 patients	US	• Patients <21 years of age at the time of initial diagnosis • Median age at study entry 12 (1–20)	• Clofarabine	• Second or subsequent relapse or were refractory to standard therapies • 57% patients refractory to last therapeutic regimen	• Amended to exclude patients with transplantation within the previous 3 months • 25% patients with one prior allo-SCT, 5% with 2 prior allo-SCTs	2–6 prior regimens, median number of prior induction therapies 3	~12 weeks

Abbreviations: AIEOP: Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem cell transplantation; DFCI: Dana Farber Cancer Institute; EFS: event-free survival; FLAG-IDA: fludarabine, cytarabine, idarubicin and G-CSF; G-CSF: granulocyte-stimulating colony factor; OS: overall survival; VXLD: Doxorubicin; SLR: systematic literature review.
Source: Miano *et al.* (2012);[96] Hijiya *et al.* (2011);[95] Locatelli *et al.* (2009);[98] Cooper *et al.* (2013);[97] Messinger *et al.* (2012);[99] Jeha *et al.* (2006).[8]

Matching-adjusted indirect treatment comparison

Due to the single-arm nature of the clinical trials investigating tisagenlecleucel and the relevant comparators (identified above), a conventional indirect treatment comparison was not possible. As such, a matching-adjusted indirect treatment comparison (MAIC) approach was used to explore adjustments of the tisagenlecleucel population to more closely match that of the von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) populations, respectively, and hence account for any impact of population differences on OS and EFS estimates.

As discussed in Section B.2.8, given the differences between tisagenlecleucel trials and that data with long-term follow-up from the pivotal ELIANA trial are now available, pooled data were not considered for inclusion in the economic model, and results for the MAIC comparison based on the ELIANA trial alone are presented below. However, for completeness, an analysis using data from the pooled tisagenlecleucel trials was conducted and resulted in similar observations, the results and methodology of this analysis can be found in Appendix D.

Versus the blinatumomab von Stackelberg *et al.* (2016) study, feedback from UK clinical experts was that it would be reasonable to conclude that patients in the blinatumomab trial were fitter based on the proportion refractory and those with >3 lines of prior therapy. Newly-identified studies (i.e. Gore *et al.* [2018], Locatelli *et al.* [2022]) were deemed less suitable than von Stackelberg *et al.* (2016) as discussed above.

Versus the salvage chemotherapy Jeha *et al.* (2006) study, UK clinical experts considered reported OS to be comparable to that expected with FLAG-IDA and efficacy with clofarabine monotherapy or clofarabine combination therapy could be considered appropriate for use as a proxy for the clinical efficacy of FLAG-IDA. Newly identified studies (i.e. Zwaan [2017], Bertaina [2017], Kuhlen [2018]), were deemed less suitable than Jeha *et al.* (2006).

Due to the limited sample size, adjusting for all patient characteristics in the MAIC is not possible. Baseline characteristics that are suspected to be effect modifying in nature were considered, with their relative importance for adjustment ranked based on previous consultation with clinicians and review of the literature. Table 23 highlights the characteristics considered and their respective ranks. A balance between precision and clinical relevance was adopted by prioritising higher ranking characteristics while ensuring sufficient effect sample size (ESS) of at least 50% of the patient population.

Table 23: Baseline characteristics considered for inclusion in the MAIC

Characteristic	Rank
Trisomy 21	High
Number of previous remissions/relapses	High
Prior HSCT	High
Number of prior lines of therapy	High
MLL total	Medium
BCR-ABL	Medium
Months since last relapse	Medium
Hypodiploidy	Medium
Blast count	Medium
Age	Low
Sex	Low

Abbreviations: BCR-ABL: breakpoint cluster region-Abelson; HSCT: haematopoietic stem cell transplant; MLL: mixed-lineage leukaemia.

An overview of the distribution of baseline characteristic before and after adjusting for comparisons between ELIANA and the two comparator studies (i.e. von Stackelberg *et al.* [2016] and Jeha *et al.* [2006]) can be found in Table 24 and Table 25 respectively. Distributions of baseline characteristics that were adjusted for were largely similar post adjustment. Due to data availability in the comparator studies and the limited sample size, it was not possible to adjust for all patient characteristics. Overall, nine variables were adjusted for in the comparison with von Stackelberg *et al.* (2016) and seven for the comparison with Jeha *et al.* (2006). The differences in variables adjusted were due largely in part to data availability in the comparator studies.

In general, whilst distribution of most patient characteristics in the ELIANA trial did not differ considerably after adjustment, there were a few instances where the changes were more substantial. For example, in the comparison with von Stackelberg *et al.* (2016), the distribution of previous remission/relapses changed considerably after matching, with a higher proportion having fewer remission/relapses than before adjustment. In the comparison with Jeha *et al.* (2006), the percentage of patients with prior HSCT was far lower after adjustments.

Table 24: Summary of baseline characteristics of ELIANA and von Stackelberg *et al.* (2016) before and after adjustment

Characteristic	Adjusted For	ELIANA		Comparator
		Before Adjustment	After Adjustment	von Stackelberg *et al.* (2016)
Trisomy 21 (%)	Yes	7.59	2.86	2.86
Previous remissions/ relapses = 0 (%)	Yes	7.59	2.86	2.86
Previous remissions/ relapses = 1 (%)	Yes	26.58	44.29	44.29
Previous remissions/ relapses = 2 (%)	Yes	21.52	41.43	41.43
Previous remissions/ relapses = 3+ (%)	Yes	44.30	11.43	11.43
Prior HSCT (%)	Yes	60.76	57.14	57.14
Number of prior lines of therapy (mean)	No	3.45	3.02	NR
MLL total (%)	No	1.27	3.64	14.29
BCR-ABL (%)	Yes	2.53	2.86	2.86
Months since last relapse (mean)	No	4.25	3.68	2.90
Hypodiploidy (%)	Yes	1.27	5.71	5.71
Blast count (%)	Yes	68.35	74.29	74.29
Age (mean)	No	12.04	11.30	8.00
Sex, male (%)	No	56.96	57.12	67.14

Abbreviations: BCR-ABL: breakpoint cluster region-Abelson; HSCT: haematopoietic stem cell transplant; MLL: mixed-lineage leukaemia; NR: not reported.
Source: ELIANA CSR (17th Nov 2022);[2] von Stackelberg *et al.* (2016).[7]

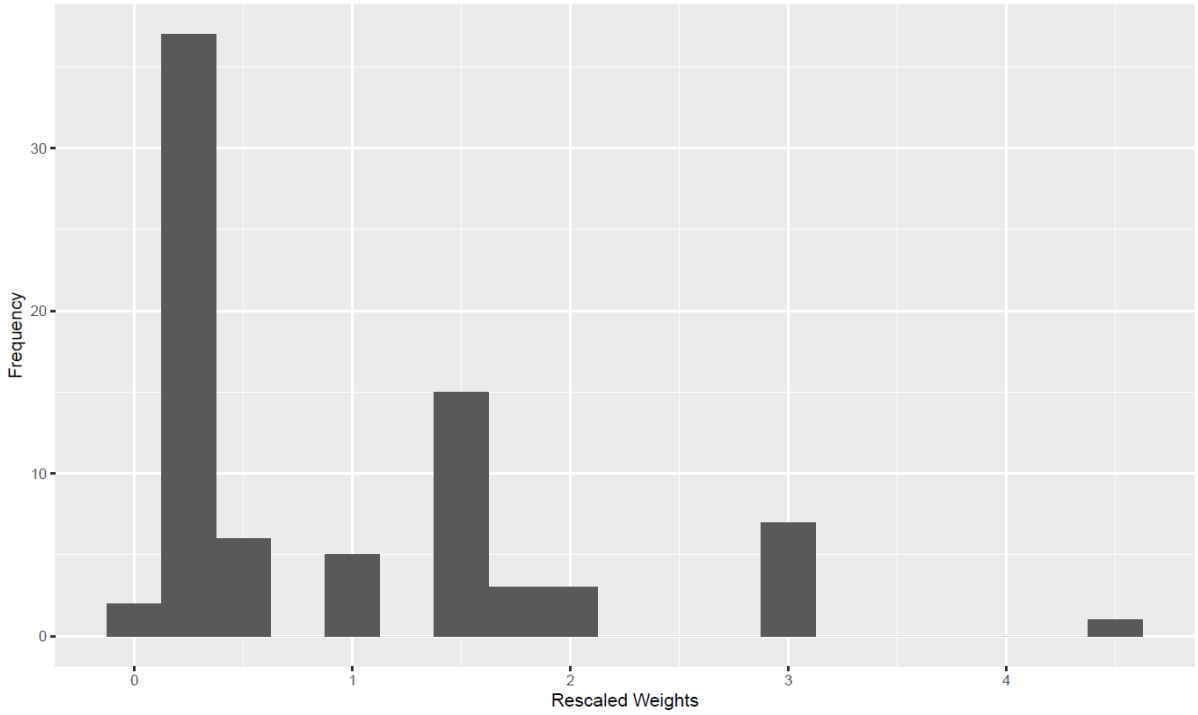
Table 25: Summary of baseline characteristics of ELIANA and Jeha *et al.* (2006) before and after adjustment

Characteristic	Adjusted For	ELIANA		Comparator
		Before Adjustment	After Adjustment	Jeha *et al.* (2006)
Trisomy 21 (%)	No	7.59	10.67	NR
Previous remissions/ relapses (mean)	No	2.35	1.88	NR
Prior HSCT (%)	Yes	60.76	29.51	29.51
Number of prior lines of therapy = 1 (%)	No	5.06	0.00	0.00
Number of prior lines of therapy = 2 (%)	Yes	27.85	37.70	37.70
Number of prior lines of therapy = 3 (%)	Yes	25.32	36.07	36.07
Number of prior lines of therapy = 4 (%)	Yes	18.99	21.31	21.31
Number of prior lines of therapy = 5 (%)	Yes	7.59	1.64	1.64
Number of prior lines of therapy = 6 (%)	Yes	15.19	3.28	3.28
MLL total (%)	No	1.27	1.42	NR
BCR-ABL (%)	Yes	2.53	4.92	4.92
Months since last relapse (mean)	No	4.25	4.06	NR
Hypodiploidy (%)	No	1.27	0.07	9.84
Blast count (%)	No	68.35	68.43	NR
Age (mean)	No	12.04	12.75	12.00
Sex, male (%)	No	56.96	56.43	60.66

Abbreviations: BCR-ABL: breakpoint cluster region-Abelson; HSCT: haematopoietic stem cell transplant; MLL: mixed-lineage leukaemia; NR: not reported.
Source: ELIANA CSR (17th Nov 2022);[2] Jeha *et al.* (2006).[8]

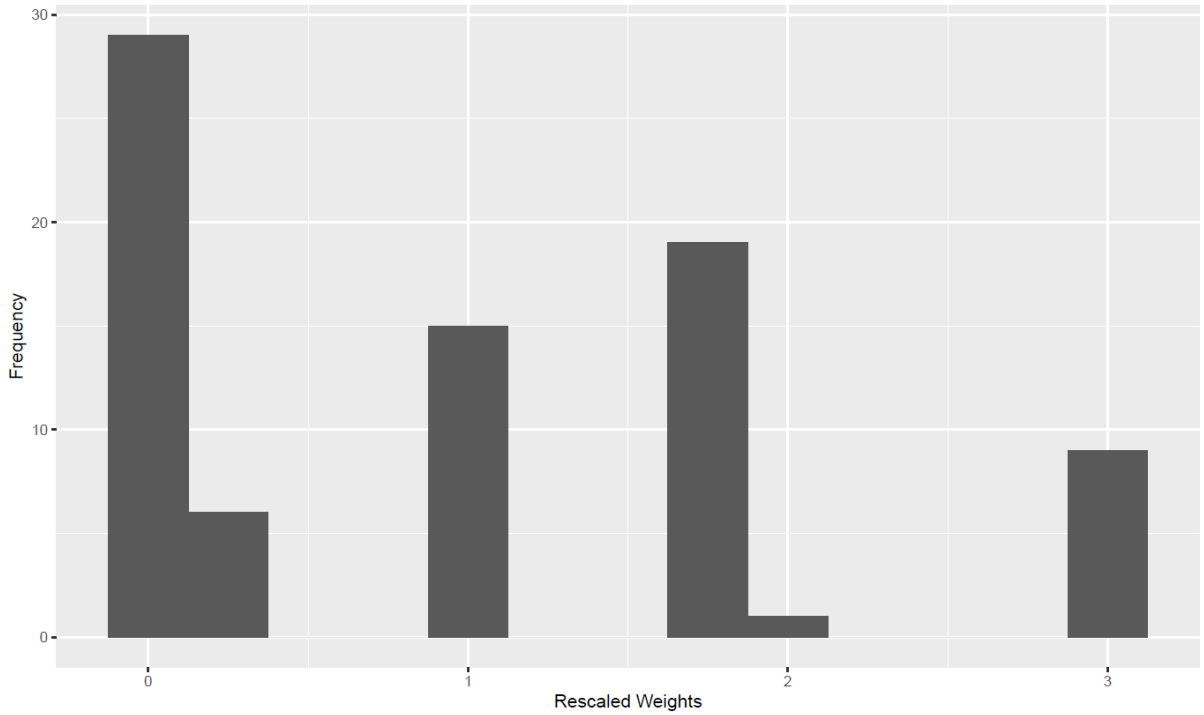
The distribution of weights of patients in ELIANA in the comparison with von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) displayed in Figure 22 and Figure 23 respectively.[7, 8, 68] Generally, there was a lack of extreme weights, and the majority of weights ranged from 0–2.

Figure 22: Distribution of weights of patients in ELIANA in the comparison with von Stackelberg *et al*. (2016)



Source: ELIANA CSR (17th Nov 2022);[2] von Stackelberg *et al.* (2016).[7]

Figure 23: Distribution of weights of patients in ELIANA in the comparison with Jeha *et al*. (2006)



Source: ELIANA CSR (17th Nov 2022);[2] Jeha *et al.* (2006).[8]

An overview of the MAIC results for OS is presented in Table 26 respectively. The OS benefit for tisagenlecleucel observed in the naïve comparison remained consistent and statistically significant

at the 95% confidence level in the MAICs. Reductions in ESS were expected given the differences between the populations but in all comparisons the proportion of the original sample size involved in the MAIC remained at >50%.

Table 26: Overall survival results

Adjustment scenario	Naïve comparison		MAIC		
	HR (95% CI)	p-value	ESS	HR (95% CI)	p-value
Tisagenlecleucel vs blinatumomab	0.26 (0.16, 0.43)	P<0.001	41.60	0.31 (0.18, 0.55)	P<0.001
Tisagenlecleucel vs salvage chemotherapy	0.14 (0.09, 0.24)	P<0.001	41.34	0.19 (0.10, 0.35)	P<0.001

Abbreviations: CI: confidence interval; ESS, effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison.
Source: ELIANA CSR (17th Nov 2022);[2] von Stackelberg *et al.* (2016); Jeha *et al.* (2006).

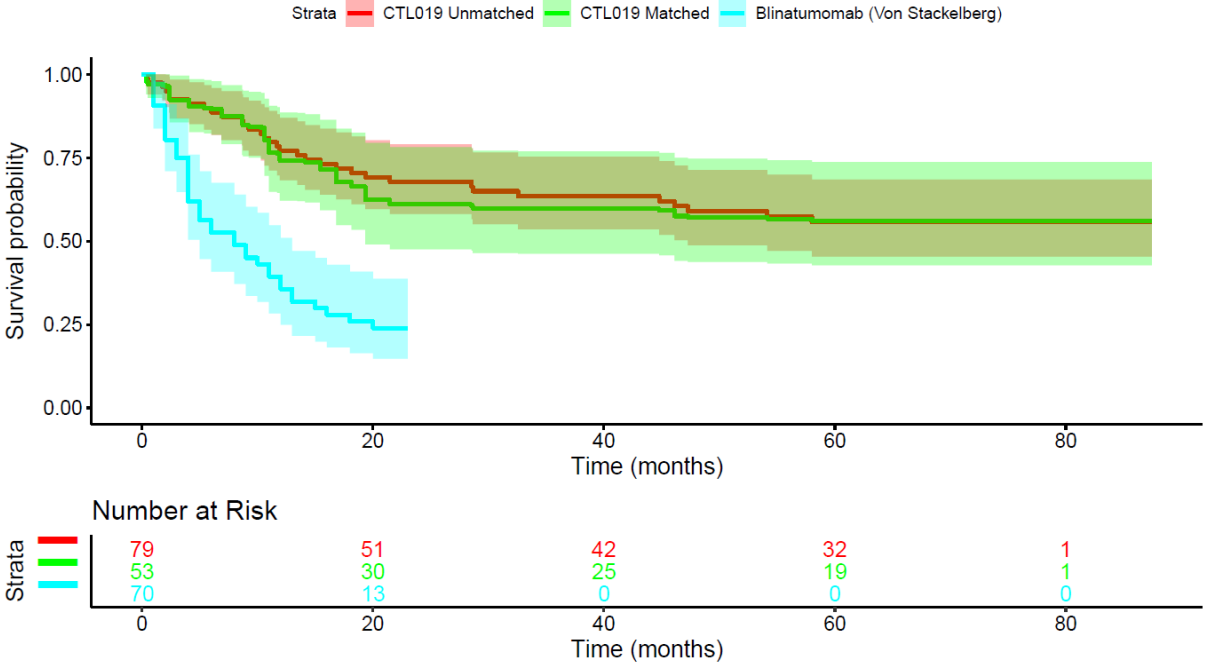
The Kaplan–Meier plot of OS for the matched and unmatched tisagenlecleucel cohorts versus blinatumomab and salvage chemotherapy are presented in Figure 24 and Figure 25 respectively. A consistent benefit in OS over time for tisagenlecleucel was observed in all comparisons.

In the comparison to blinatumomab and salvage chemotherapy, the matched and unmatched curves were seen to be very similar, with the matched curves associated with a slightly lower plateau than the unmatched curves.

In all comparisons, the 95% confidence intervals of the matched and unmatched tisagenlecleucel curves overlapped substantially, indicating that differences between the matched and unmatched curves may reflect uncertainty inherent in the sample estimates rather than a true difference in efficacy.

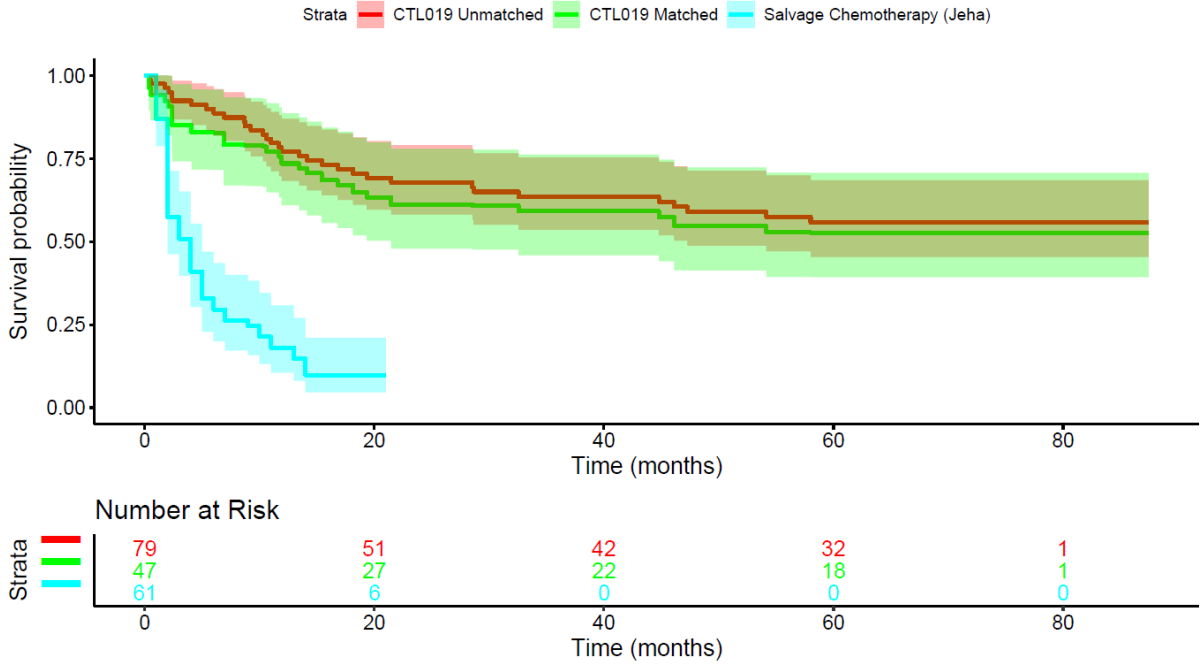
Given the lack of meaningful differences in efficacy estimates when adjusting for population differences across intervention and comparator trials, unadjusted ELIANA data were used in the economic analysis, in order to retain the largest sample sizes to inform efficacy outcomes in the model.

Figure 24: Overall survival for tisagenlecleucel versus blinatumomab



Shaded regions represent 95% CIs.
Abbreviations: CI: confidence interval; CTL019: tisagenlecleucel
Source: ELIANA CSR (17th Nov 2022);[2] von Stackelberg *et al.* (2016).[7]

Figure 25: Overall survival for tisagenlecleucel versus salvage chemotherapy



Shaded regions represent 95% CIs.
Abbreviations: CI: confidence interval; CTL019, tisagenlecleucel
Source: ELIANA CSR (17th Nov 2022);[2] Jeha *et al.* (2006).[8]

B.2.10 *Adverse reactions*

The safety and tolerability of tisagenlecleucel for the treatment of paediatric and young adult patients with r/r B-cell ALL was evaluated as a secondary outcome in both ELIANA and ENSIGN, and as part of the primary outcome of B2101J.

In all three trials, the safety population included all patients who received at least one infusion of tisagenlecleucel. The assessment of safety was based mainly on the proportion of patients reporting AEs, serious AEs (SAEs), AE of special interest (AESI), deaths, pregnancies and immunogenicity.

Safety in the ELIANA trial was assessed by monitoring and recording potential AEs using MedDRA version 20.0 and the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In the ENSIGN trial, reporting of AEs was based on MedDRA version 19.0 and CTCAE version 4.03. In B2101J, AEs were reported using MedDRA version 19.1 and CTCAE version 3.0. In all trials, the grading of cytokine release syndrome (CRS) and graft-versus-host disease (GVHD) was based on protocol-specific grading scales

B.2.10.1 Treatment duration and dosage

In ELIANA, 79 patients (81.4%) out of the 97 patients enrolled were able to receive tisagenlecleucel which was administered as a single intravenous infusion with a target dose range of 2.0 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) or of 1.0 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg).[12] Of the 79 patients that received tisagenlecleucel, 70 patients (88.6%) received tisagenlecleucel doses within the protocol-specified target dose range. Two patients (2.5%) received a dose above the target range and seven patients (8.9%) received a dose below the target range. The median total tisagenlecleucel dose infused was 1.00×10^8 cells (range 0.03 to 2.60×10^8) and the median weight-adjusted tisagenlecleucel dose infused was 3.00×10^6 cells/kg (range 0.2 to 5.4×10^6).[2]

In ENSIGN, 64 patients (85.3%) out of the 75 patients enrolled were able to receive tisagenlecleucel which was administered as a single intravenous infusion with a target dose equivalent to the ELIANA trial with a range of 2.0 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) or of 1.0 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg). Of the 64 patients that received tisagenlecleucel, 52 patients (81.3%) received tisagenlecleucel doses within the protocol-specified target dose range as specified above and 12 patients (18.8%) received a below target dose range. The median total tisagenlecleucel dose infused was 1.15×10^8 cells (range 0.09×10^8 to 2.50×10^8) and the median weight-adjusted tisagenlecleucel dose infused was 3.40×10^6 cells/kg (range 0.2×10^6 to 5.0×10^6).[6]

In the B2101J trial, 57 patients of the 67 patients enrolled were able to receive tisagenlecleucel which was administered according to a dose escalation schedule (10% on Day 0, 30% on Day 1, and possible escalation of 60% on Day 14 or later, with necessary protocol-specified adjustments where appropriate) with a maximum total dose target range of 1.5×10^7 to 5×10^9 total cells. Full details of any protocol-specific dose adjustments received can be found in the CSR for B2101J.[62] The median total tisagenlecleucel dose infused during the overall study was 3.3×10^8 cells (range 0.1×10^8 to 11.4×10^8) and the median weight-adjusted tisagenlecleucel dose infused during the overall study was 7.5×10^6 cells/kg (range 0.6×10^6 to 22.6×10^6).[5]

B.2.10.2 Safety analysis in the relevant clinical trials

A summary of the safety results from the ELIANA, ENSIGN and B2101J clinical trials is presented in Table 27 below. Across all three trials, as of the latest data cuts reported in this submission, a total of 79, 64 and 57 patients had received infusion with tisagenlecleucel and were analysed in the safety sets of ELIANA, ENSIGN and B2101J, respectively.[2, 5, 6]

Table 27: Overall summary of AEs in ELIANA, ENSIGN and B2101J (safety set)

Adverse event, n (%)	ELIANA (safety set) (N=79)	ENSIGN (safety set) (N=64)	B2101J (safety set) (N=57)[a]
Number of patients with at least one AE	79 (100)	64 (100)	57 (100)
Suspected to be study drug-related	75 (94.9)	62 (96.9)	57 (100)
Death within 30 days post-tisagenlecleucel infusion	2 (2.5)	2 (3.1)	3 (5.3)[b]
Death >30 days post-tisagenlecleucel infusion	31 (39.2)	28 (43.8)	24 (42.1)[c]
Patients with serious or other significant events			
Any time post-tisagenlecleucel infusion			
SAE	63 (79.7)	52 (81.3)	52 (91.2)
SAE suspected to be study drug-related	53 (67.1)	46 (71.9)	49 (86.0)
Grade 3/4 AE	72 (91.1)	59 (92.2)	55 (96.5)
Grade 3/4 AE suspected to be study drug-related	59 (74.7)	52 (81.3)	55 (96.5)
Within 8 weeks post-tisagenlecleucel infusion			
SAE	54 (68.4)	46 (71.9)	-
SAE suspected to be study drug-related	52 (65.8)	44 (68.8)	-
Grade 3/4 AE	66 (83.5)	54 (84.4)	-
Grade 3/4 AE suspected to be study drug-related	56 (70.9)	49 (76.6)	-
>8 weeks post-tisagenlecleucel infusion			
	(N=74)	**(N=56)**	
SAE	31 (41.9)	24 (42.9)	-
SAE suspected to be study drug-related	6 (8.1)	8 (14.3)	-
Grade 3/4 AE	45 (60.8)	31 (55.4)	-
Grade 3/4 AE suspected to be study drug-related	15 (20.3)	14 (25.0)	-

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b]In the B2101J trial, this refers to deaths within 30 days of the last infusion of tisagenlecleucel (no deaths occurred within 30 days of the first infusion).
[c]Value calculated based on 27 deaths post-tisagenlecleucel infusion, and three of these occurring within 30 days of the last infusion. Therefore, 24 occurred 30 days after the last infusion (42.1% of 57).
All deaths during both study follow-up and survival follow-up are summarised.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

Deaths

A total of 33 deaths (41.8%) occurred in the ELIANA trial post-tisagenlecleucel infusion (DCO 17th Nov 2022).[2] Two patients died within 30 days post-tisagenlecleucel infusion of which one due to intracranial haemorrhage and one due to underlying disease progression. The other 31 deaths occurred more than 30 days post-tisagenlecleucel infusion. Of these, 24 deaths (30.4%) were attributed to underlying disease progression, one was due to viral encephalitis, one due to

systemic mycosis, one due to lung infection (bacterial pneumonia), one due to hepatobiliary disease, one due to GVHD, one due to multiple organ dysfunction syndrome and COVID-19 infection and one due to an unknown reason.[2]

A total of 30 deaths (46.9%) occurred in the ENSIGN trial post-tisagenlecleucel infusion (DCO 24th May 2019). Two patients died within 30 days post-tisagenlecleucel infusion; one due to underlying disease progression and one due to embolic stroke. The other 28 deaths occurred more than 30 days post-tisagenlecleucel infusion. Of these, 24 deaths (37.5%) were attributed to underlying disease progression, one due to complications of transplant surgery, one due to glioblastoma multiforme, one due to seizure and one due to sepsis.[6]

A total of 27 deaths (47.4%) occurred in the B2101J trial post-tisagenlecleucel infusion (DCO 7th May 2018). No deaths were reported within 30 days after the first tisagenlecleucel infusion, whereas three patients (5.3%) died within 30 days after the final tisagenlecleucel infusion, and 24 patients (42.1%) died more than 30 days after the last tisagenlecleucel infusion.[5]

AEs post-tisagenlecleucel infusion, regardless of study drug relationship

AEs regardless of study drug relationship occurred in 100% patients in ELIANA, ENSIGN and B2101J.[2, 5, 6] In the ELIANA trial, regardless of study drug relationship, the most frequent AEs overall were CRS, pyrexia, hypogammaglobulinaemia and decreased appetite, which occurred in at any grade in 77.2%, 44.3%, 40.5% and 38.0% patients, respectively.[2] CRS was also the most common AE regardless of study drug relationship in ENSIGN, followed by a decreased white blood cell count, hypogammaglobulinaemia and decreased neutrophil count. These AEs occurred in 78.1%, 54.7%, 50.0% and 43.8% patients, respectively.[6] Lastly, in B2101J, decreased white blood cell count was the most common AE regardless of study drug relationship, occurring in 94.7% patients. The next most common AEs were a decrease in haemoglobin, a decreased neutrophil count and CRS, occurring in 93.0%, 91.2% and 89.5% patients, respectively.[62]

A summary of frequently reported AEs post-tisagenlecleucel infusion, regardless of study drug relationship for all three trials is presented in Table 28.

Table 28: Summary of AEs reported in ≥10% of patients post-tisagenlecleucel infusion, regardless of study drug relationship (safety set)

	ELIANA (safety set) (N=79)			ENSIGN (safety set) (N=64)			B2101J (safety set) (N=57)[a]		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one AE	**79 (100)**	**18 (22.8)**	**54 (68.4)**	**64 (100)**	**12 (18.8)**	**47 (73.4)**	**57 (100)**	**11 (19.3)**	**44 (77.2)**
CRS	61 (77.2)	17 (21.5)	21 (26.6)	50 (78.1)	8 (12.5)	11 (17.2)	51 (89.5)	12 (21.1)	14 (24.6)
Pyrexia	35 (44.3)	9 (11.4)	2 (2.5)	25 (39.1)	6 (9.4)	1 (1.6)	20 (35.1)	1 (1.8)	0
Decreased appetite	30 (38.0)	10 (12.7)	2 (2.5)	22 (34.4)	12 (18.8)	0	39 (68.4)	20 (35.1)	0
Hypogammaglobulinaemia	32 (40.5)	6 (7.6)	0	32 (50.0)	5 (7.8)	0	38 (66.7)	0	0
Febrile neutropenia	27 (34.2)	25 (31.6)	2 (2.5)	24 (37.5)	23 (35.9)	1 (1.6)	45 (78.9)	37 (64.9)	8 (14.0)
Headache	27 (34.2)	3 (3.8)	0	24 (37.5)	2 (3.1)	0	43 (75.4)	8 (14.0)	0
Anaemia	25 (31.6)	9 (11.4)	0	27 (42.2)	19 (29.7)	1 (1.6)	-	-	-
Vomiting	26 (32.9)	1 (1.3)	0	27 (42.2)	3 (4.7)	0	44 (77.2)	4 (7.0)	0
Platelet count decreased	24 (30.4)	7 (8.9)	8 (10.1)	20 (31.3)	3 (4.7)	12 (18.8)	50 (87.7)	8 (14.0)	20 (35.1)
White blood cell count decreased	24 (30.4)	1 (1.3)	16 (20.3)	35 (54.7)	12 (18.8)	18 (28.1)	54 (94.7)	19 (33.3)	18 (31.6)
Hypotension	24 (30.4)	8 (10.1)	8 (10.1)	16 (25.0)	7 (10.9)	8 (12.5)	29 (50.9)	3 (5.3)	15 (26.3)
Neutrophil count decreased	24 (30.4)	4 (5.1)	17 (21.5)	28 (43.8)	4 (6.3)	21 (32.8)	52 (91.2)	14 (24.6)	26 (45.6)
Diarrhoea	26 (32.9)	2 (2.5)	0	24 (37.5)	2 (3.1)	0	32 (56.1)	1 (1.8)	0
Nausea	22 (27.8)	2 (2.5)	0	25 (39.1)	5 (7.8)	0	42 (73.7)	8 (14.0)	0
Hypokalaemia	20 (25.3)	9 (11.4)	2 (2.5)	19 (29.7)	8 (12.5)	1 (1.6)	-	-	-
Hypoxia	20 (25.3)	10 (12.7)	6 (7.6)	10 (15.6)	4 (6.3)	3 (4.7)	-	-	-
Aspartate aminotransferase increased	19 (24.1)	8 (10.1)	3 (3.8)	20 (31.3)	8 (12.5)	4 (6.3)	42 (73.7)	12 (21.1)	4 (7.0)
Cough	23 (29.1)	0	0	14 (21.9)	0	0	32 (56.1)	0	0
Alanine aminotransferase increased	18 (22.8)	7 (8.9)	0	21 (32.8)	14 (21.9)	0	41 (71.9)	13 (22.8)	4 (7.0)

Hypophosphataemia	18 (22.8)	8 (10.1)	1 (1.3)	10 (15.6)	7 (10.9)	1 (1.6)	-	-	-
Lymphocyte count decreased	17 (21.5)	10 (12.7)	5 (6.3)	16 (25.0)	7 (10.9)	5 (7.8)	-	-	-
Tachycardia	17 (21.5)	2 (2.5)	1 (1.3)	15 (23.4)	2 (3.1)	0	27 (47.4)	0	1 (1.8)
Fatigue	17 (21.5)	0	0	15 (23.4)	1 (1.6)	0	25 (43.9)	0	0
Hypocalcaemia	16 (20.3)	5 (6.3)	0	-	-	-	-	-	-
Hypertension	16 (20.3)	5 (6.3)	0	12 (18.8)	1 (1.6)	0	-	-	-
Pain in extremity	17 (21.5)	1 (1.3)	0	11 (17.2)	0	0	-	-	-
Constipation	14 (17.7)	0	0	7 (10.9)	0	0	-	-	-
Anxiety	14 (17.7)	2 (2.5)	0	7 (10.9)	1 (1.6)	0	-	-	-
Blood bilirubin increased	13 (16.5)	9 (11.4)	0	8 (12.5)	3 (4.7)	0	-	-	-
Acute kidney injury	12 (15.2)	3 (3.8)	5 (6.3)	9 (14.1)	4 (6.3)	3 (4.7)	-	-	-
Pulmonary oedema	12 (15.2)	6 (7.6)	1 (1.3)	7 (10.9)	4 (6.3)	2 (3.1)	-	-	-
Upper respiratory tract infection	13 (16.5)	3 (3.8)	0	9 (14.1)	1 (1.6)	0	-	-	-
Abdominal pain	11 (13.9)	2 (2.5)	0	11 (17.2)	1 (1.6)	0	18 (31.6)	2 (3.5)	0
Hypoalbuminaemia	11 (13.9)	1 (1.3)	0	-	-	-	-	-	-
Neutropenia	11 (13.9)	2 (2.5)	7 (8.9)	11 (17.2)	3 (4.7)	8 (12.5)	-	-	-
Back pain	10 (12.7)	3 (3.8)	0	-	-	-	-	-	-
Myalgia	10 (12.7)	0	0	-	-	-	-	-	-
Hyperuricaemia	9 (11.4)	1 (1.3)	0	-	-	-	-	-	-
International normalised ratio increased	9 (11.4)	0	0	9 (14.1)	1 (1.6)	0	-	-	-
Nasal congestion	9 (11.4)	0	0	-	-	-	-	-	-
Thrombocytopenia	9 (11.4)	3 (3.8)	6 (7.6)	10 (15.6)	3 (4.7)	6 (9.4)	-	-	-
Arthralgia	12 (15.2)	1 (1.3)	0	-	-	-	-	-	-
Delirium	8 (10.1)	3 (3.8)	0	-	-	-	-	-	-
Disseminated intravascular coagulation	8 (10.1)	3 (3.8)	0	-	-	-	-	-	-

Encephalopathy	8 (10.1)	4 (5.1)	0	-	-	-	-	-	-
Hyperglycaemia	9 (11.4)	5 (6.3)	0	-	-	-	-	-	-
Pleural effusion	9 (11.4)	2 (2.5)	1 (1.3)	8 (12.5)	2 (3.1)	0	-	-	-
Rhinovirus infection	9 (11.4)	2 (2.5)	0	-	-	-	-	-	-
Serum ferritin increased	8 (10.1)	2 (2.5)	0	-	-	-	-	-	-
Tachypnoea	9 (11.4)	4 (5.1)	1 (1.3)	-	-	-	-	-	-
Dry skin	8 (10.1)	0	0	-	-	-	-	-	-
Face oedema	8 (10.1)	1 (1.3)	0	-	-	-	-	-	-
Oropharyngeal pain	8 (10.1)	0	0	-	-	-	-	-	-
Conjunctivitis	8 (10.1)	0	0	-	-	-	-	-	-
Blood creatinine increased	-	-	-	9 (14.1)	2 (3.1)	0	20 (35.1)	1 (1.8)	0
Prothrombin time prolonged	-	-	-	9 (14.1)	1 (1.6)	0	-	-	-
Chills	-	-	-	10 (15.6)	0	0	23 (40.4)	0	0
Epistaxis	-	-	-	10 (15.6)	4 (6.3)	1 (1.6)	-	-	-
Hyperphosphataemia	-	-	-	8 (12.5)	0	0	19 (33.3)	0	0
Rash	8 (10.1)	0	0	8 (12.5)	0	0	-	-	-
Haemoglobin decreased	-	-	-	-	-	-	53 (93.0)	13 (22.8)	4 (7.0)
Lymphopenia	-	-	-	-	-	-	47 (82.5)	19 (33.3)	20 (35.1)
Pain	-	-	-	-	-	-	27 (47.4)	7 (12.3)	0
Activated partial thromboplastin time prolonged	-	-	-	-	-	-	19 (33.3)	5 (8.8)	0

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
AEs reported in at least 10% patients in the ELIANA and ENSIGN trials, and in at least 30% patients in B2101J. A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
Abbreviations: AE: adverse event; CRS: cytokine release syndrome.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018);[5] Laetsch *et al.* (2022).[12]

AEs post-tisagenlecleucel infusion suspected to be study drug related

In all three trials, the vast majority of patients reported AEs that were suspected to be related to the infusion of tisagenlecleucel. Overall, 94.9%, 96.9% and 100% patients experienced a tisagenlecleucel-related AE in the ELIANA, ENSIGN and B2101J trials, respectively.[2, 5, 6] A summary of AEs suspected to be study drug-related reported post-tisagenlecleucel infusion for all three trials is presented in Appendix F.

SAEs post-tisagenlecleucel infusion, regardless of study drug relationship

SAEs post tisagenlecleucel infusion and regardless of study drug relationship were reported in 63 (79.7%), 52 (81.3%) and 52 (91.2%) patients in the ELIANA, ENSIGN and B2101J trials, respectively.[2, 5, 6] In all three trials, the most common SAEs regardless of study drug relationship were CRS, febrile neutropenia and hypotension occurring in 63.3%, 19.0% and 10.1% in ELIANA, 64.1%, 35.9% and 10.9% in ENSIGN and 82.5%, 71.9% and 38.6% in B2101J, respectively.[2, 5, 6] SAEs were managed by standard supportive care procedures and concomitant medications and when indicated, anti-cytokine therapy per the protocol-defined CRS algorithm in a hospital setting.

A summary of SAEs regardless of study drug relationship for all three trials is presented in Table 29.

Table 29: Summary of SAEs reported in at least two patients post-tisagenlecleucel infusion, regardless of study drug relationship (safety set)

	ELIANA (safety set) (N=79)			ENSIGN (safety set) (N=64)			B2101J (safety set) (N=57)[a]		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one SAE	63 (79.7)	23 (29.1)	37 (46.8)	52 (81.3)	21 (32.8)	24 (37.5)	52 (91.2)	30 (52.6)	19 (33.3)
CRS	50 (63.3)	16 (20.3)	21 (26.6)	41 (64.1)	8 (12.5)	10 (15.6)	47 (82.5)	11 (19.3)	14 (24.6)
Febrile neutropenia	15 (19.0)	14 (17.7)	1 (1.3)	23 (35.9)	22 (34.4)	1(1.6)	41 (71.9)	33 (57.9)	8 (14.0)
Hypotension	8 (10.1)	1 (1.3)	7 (8.9)	7 (10.9)	4 (6.3)	3 (4.7)	22 (38.6)	3 (5.3)	15 (26.3)
Pyrexia	7 (8.9)	1 (1.3)	0	7 (10.9)	1(1.6)	0	13 (22.8)	1 (1.8)	0
Acute kidney injury	5 (6.3)	2 (2.5)	3 (3.8)	4 (6.3)	3 (4.7)	1 (1.6)	3 (5.3)	2 (3.5)	0
Hypoxia	5 (6.3)	3 (3.8)	2 (2.5)	4 (6.3)	1 (1.6)	1 (1.6)	8 (14.0)	5 (8.8)	3 (5.3)
Respiratory failure	5 (6.3)	0	5 (6.3)	3 (4.7)	0	3 (4.7)	1 (1.8)	0	0 (1.8)
Back pain	3 (3.8)	2 (2.5)	0	-	-	-	-	-	-
Cardiac arrest	3 (3.8)	0	3 (3.8)	-	-	-	1 (1.8)[b]	0[b]	1(1.8)[b]
Disseminated intravascular coagulation	3 (3.8)	2 (2.5)	0	2 (3.1)	0	0	5 (8.8)	3 (5.3)	0
Acute respiratory distress syndrome	2 (2.5)	0	2 (2.5)	-	-	-	4 (7.0)	0	4 (7.0)
Aspartate aminotransferase increased	2 (2.5)	2 (2.5)	0	-	-	-	-	-	-
Cardiac failure	2 (2.5)	1 (1.3)	1 (1.3)	-	-	-	-	-	-
Diarrhoea	2 (2.5)	1 (1.3)	0	2 (3.1)	0	0	-	-	-
Encephalitis	2 (2.5)	0	2 (2.5)	-	-	-	-	-	-
Viral encephalitis	2 (2.5)	1 (1.3)	1 (1.3)	-	-	-	-	-	-
Gastroenteritis	2 (2.5)	2 (2.5)	0	-	-	-	1 (1.8)[c]	1 (1.8)[c]	0[c]

Herpes zoster	2 (2.5)	2 (2.5)	0	-	-	-	-	-	-
Mental status changes	2 (2.5)	1 (1.3)	0	-	-	-	1 (1.8)	0	0
Multiple organ dysfunction syndrome	3 (3.8)	0	3 (3.8)	-	-	-	-	-	-
Pancreatitis	2 (2.5)	2 (2.5)	0	-	-	-	-	-	-
Pleural effusion	2 (2.5)	1 (1.3)	1 (1.3)	2 (3.1)	1 (1.6)	0	1 (1.8)	0	1 (1.8)
Pneumonia	2 (2.5)	1 (1.3)	1 (1.3)	2 (3.1)	1 (1.6)	0	-	-	-
Respiratory distress	2 (2.5)	0	1 (1.3)	-	-	-	1 (1.8)	0	1 (1.8)
Respiratory syncytial virus infection	2 (2.5)	2 (2.5)	0	-	-	-	-	-	-
Rhinovirus infection	2 (2.5)	1 (1.3)	0	-	-	-	-	-	-
Septic shock	2 (2.5)	0	2 (2.5)	-	-	-	-	-	-
Staphylococcal bacteraemia	2 (2.5)	2 (2.5)	0	-	-	-	1 (1.8)	1 (1.8)	0
Tumour lysis syndrome	2 (2.5)	1 (1.3)	1 (1.3)	2 (3.1)	2 (3.1)	0	1 (1.8)	1 (1.8)	0
Upper respiratory tract infection	3 (3.8)	3 (3.8)	0	-	-	-	-	-	-
Clostridium difficile infection	-	-	-	3 (4.7)	1 (1.6)	0	-	-	-
Seizure	-	-	-	4 (6.3)	2 (3.1)	0	3 (5.3)	0	1 (1.8)
Encephalopathy	-	-	-	4 (6.3)	2 (3.1)	0	15 (26.3)	13 (22.8)	0
Neutropenia	-	-	-	3 (4.7)	0	3 (4.7)	-	-	-
Clostridium difficile colitis	-	-	-	2 (3.1)	0	0	-	-	-
Pulmonary oedema	-	-	-	2 (3.1)	1 (1.6)	1 (1.6)	-	-	-
Capillary leak syndrome	-	-	-	-	-	-	10 (17.5)	1 (1.8)	9 (15.8)
Dehydration	-	-	-	1 (1.6)	1 (1.6)	0	4 (7.0)	1 (1.8)	0

Left ventricular dysfunction	-	-	-	-	-	-	4 (7.0)	2 (3.5)	0
Coagulopathy	-	-	-	-	-	-	3 (5.3)	3 (5.3)	0
Device related infection	-	-	-	-	-	-	2 (3.5)	1 (1.8)	1 (1.8)
Headache	2 (2.5)	2 (2.5)	0	-	-	-	2 (3.5)	1 (1.8)	0
Sepsis	3 (3.8)	1 (1.3)	2 (2.5)	1 (1.6)	0	1 (1.6)	-	-	-
Candida infection	2 (2.5)	0	1 (1.3)	-	-	-	-	-	-
Hemophagocytic lymphohistiocytosis	2 (2.5)	0	2 (2.5)	-	-	-	-	-	-
Urinary tract infection	-	-	-	2 (3.1)	1 (1.6)	0	-	-	-

For SAEs which were presented in at least two patients in any of the three tisagenlecleucel trials, the occurrence of the same SAE in the other trials were also extracted regardless of the number of cases reported (i.e. <2 cases).
[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only. In the ELIANA and ENSIGN trials, SAEs are reported when they occurred in at least two patients, whereas in the B2101J trial, SAEs are reported if they occurred in at least 5% patients. A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
[b]Reported as cardio-respiratory arrest.
[c]Reported as gastroenteritis salmonella.
Abbreviations: CRS: cytokine release syndrome; NR: not reported; SAE: serious adverse event.
Source: ELIANA CSR (17th Nov 2022);[2] ENSIGN CSR (24th May 2019);[6] B2101J CSR (7th May 2018).[5]

SAEs post-tisagenlecleucel infusion suspected to be study drug related

In all three trials, the majority of patients reported SAEs that were suspected to be related to the infusion of tisagenlecleucel. Overall, 67.1%, 71.9% and 86.0% patients experienced a tisagenlecleucel-related SAE in the ELIANA, ENSIGN and B2101J trials, respectively. [2, 5, 6] A summary of SAEs suspected to be study drug-related reported post-tisagenlecleucel infusion for all three trials is presented in Appendix F.

Cytokine release syndrome

ELIANA

CRS in the ELIANA trial was assessed via the Penn Grading Scale for CRS (PGS-CRS). Of the 79 patients infused with tisagenlecleucel, 61 (77.2%) patients had CRS. [51] The median time to onset of CRS was 3.0 days (range: 1–22 days). Of note, 38/61 (62.3%) cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[51]

Among the 61 patients with CRS, the median duration of CRS was 7.5 days (range: 1–36 days). 38 patients (48.1%) were admitted to the intensive care unit (ICU) for a median duration of 7.0 days (range: 1–66 days) and a mean (SD) duration of 11.1 (12.09) days. 31 patients (39.2%) with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, siltuximab, corticosteroids or other therapies (e.g. infliximab, etanercept). Among all infused patients, one, two, and three doses of tocilizumab were required in 18 (22.8%), 10 (12.7%), and three (3.8%) patients, respectively, and 17 patients (21.5%) received corticosteroids in addition to tocilizumab. 19 patients required high-dose vasopressors, 12 patients required invasive ventilation, and eight patients required dialysis.[51]

ENSIGN

CRS in the ENSIGN trial was assessed via the Penn Grading Scale for CRS (PGS-CRS). Of the 64 patients infused with tisagenlecleucel, 50 (78.1%) had CRS. The median time to onset of CRS was 4.5 days (range: 1–20 days). Of note, 19/50 (38.0%) cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[54]

Among the 50 patients with CRS, the median duration of CRS was 8.0 days (range: 2–33 days). 20 patients (40.0%) were admitted to the ICU for a median duration of 9.0 days (range: 1–27 days) and a mean (SD) duration of 9.9 (7.53) days. 13 patients (26.0%) with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, corticosteroids or other therapies. One, two, and three doses of tocilizumab were required in five (10.0%), four (8.0%), and three (6.0%) patients, respectively, and nine patients (18.0%) received corticosteroids in addition to tocilizumab. 12 patients required high-dose vasopressors, six patients required invasive ventilation, and four patients required dialysis.[54]

B2101J

CRS in B2101J was assessed via the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale. Of the 57 patients infused with tisagenlecleucel, 51 (89.5%) had CRS. The median time to onset of CRS was 3.0 days (range: 1–656.0 days). Of note, 23/57 (40.4%) cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[57]

Among the 51 patients with CRS, the median duration of CRS was 7.0 days (range: 2–18 days). 20 patients (39.2%) were admitted to the ICU for a median duration of 8.5 days (range: 1–90

days) and a mean (SD) duration of 13.1 (19.04) days. 16 patients (31.4%) with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, siltuximab, corticosteroids or other therapies. One and two doses of tocilizumab were required in 10 (19.6%) and 5 (9.8%) patients, respectively, and nine patients (17.6%) received corticosteroids in addition to tocilizumab. Nine patients required high-dose vasopressors, six patients required invasive ventilation, and none required dialysis.[57]

The ICU length of stay observed across all three tisagenlecleucel clinical trials is believed to be a conservative estimate of real world use since it was initially believed that tocilizumab had a detrimental effect on the efficacy of CAR-T cells. Throughout the course of the clinical trials, evidence emerged to the contrary and investigators became willing to administer tocilizumab more readily thereby preventing CRS progression and reducing the requirement for ICU admissions.

B.2.11 *Ongoing studies*

All three tisagenlecleucel clinical trials (ELIANA, ENSIGN and B2101J) have been completed. Data from the latest data cut-offs for each trial have been presented in this submission. There is an ongoing long-term follow-up study on CAR-T therapies (PAVO; NCT02445222) aimed at collecting safety and efficacy data (follow-up of 15 years) on patients who have received CAR-T therapy, regardless of indication.[100]

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Unmet need in r/r B-cell ALL

Accounting for a third of all childhood cancer, ALL contributes significantly to the burden of paediatric cancer in the UK. Paediatric and young adult patients with r/r B-cell ALL have limited licensed treatment options, as outlined in Section B.1.3.2. While the CR rates for newly diagnosed patients treated with conventional first-line chemotherapy are high at 80–85%, approximately 15–20% of patients subsequently experience disease relapse.[24-27] With every subsequent disease relapse, the chances of patients achieving CR are significantly reduced: 44% (second relapse), 27% (third relapse), and 12% (fourth or later relapse).[28] A small proportion of patients also experience refractory disease who remain severely limited in their treatment options.[13]

Being a disease that affects paediatrics and young adults, the impact of r/r B-cell ALL is especially severe, affecting patients, parents/caregivers and wider support networks. The burden of disease is exacerbated by the poor clinical outcomes, HRQoL and psychosocial outcomes associated with current treatment options for r/r B-cell ALL.[21, 30, 31] With prognosis and treatment options deteriorating at each treatment line, there remains a critical unmet need for the routine commissioning of effective treatment options that offer substantial life extension and potential for cure thereby alleviating disease burden and improving quality of life of both patients and parents/caregivers.

Tisagenlecleucel use following reimbursement via CDF

Following its reimbursement via the CDF, tisagenlecleucel has become an established treatment option as part of SOC, offering paediatric and young adult patients with r/r B-cell ALL the potential for a cure, as demonstrated by its proven effectiveness in achieving long-term remission and confirmed by clinical feedback received as part of this appraisal.[4] The recommendation for

routine commissioning of tisagenlecleucel in r/r B-cell ALL for patients aged up to 25 years would ensure that this patient population continues to benefit from access to curative options, as indicated by its established usage in current clinical practice.[4]

Key clinical uncertainties raised in original appraisal (TA554)

Clinical uncertainties highlighted by the committee and ERG in the original NICE appraisal (TA554) have been addressed in this submission, through the inclusion of longer follow-up data and revised analyses.[1] The lack of mature EFS and OS results was highlighted as a key clinical uncertainty in determining the clinical effectiveness of tisagenlecleucel and a longer follow-up period of at least five years was recommended for considering the curative intent of tisagenlecleucel.[9]

At the time of the original submission (TA554), data from ELIANA (DCO 25th Apr 2017) was limited by its short median duration from infusion to data cut-off of 13.1 months. The latest data cut-off (17th Nov 2022) presented in this submission has a median duration from infusion of 79.4 months.

In the original submission, given short-term follow-up from the pivotal ELIANA trial, data were pooled across tisagenlecleucel trials (ELIANA, ENSIGN and B2101J) to inform survival for tisagenlecleucel in the economic model. The Committee raised concerns regarding differences between these trials, particularly that patients in B2101J had higher Karnofsky/Lanksy performance status compared to patients in ELIANA and ENSIGN trials, were more likely to have received a prior allo-SCT and were eligible for multiple tisagenlecleucel infusions.[1] Given the availability of data with long-term follow-up, survival for tisagenlecleucel in the economic model for this submission was based on the ELIANA trial alone, the pivotal trial that informed the marketing authorisation for tisagenlecleucel in this indication and the trial considered most generalisable to the intended patient population and use of tisagenlecleucel in UK clinical practice.[9] Considering the size of the target population and rare nature of r/r B-cell ALL, the robustness of the data presented within this submission can be regarded as comprehensive and compelling.

Principal findings from the clinical evidence base

Evidence from tisagenlecleucel clinical trials

Evidence for the efficacy and safety of tisagenlecleucel as a treatment for paediatric and young adult patients with r/r B-cell ALL is provided from the ELIANA, ENSIGN and B2101J trials, three complete, single-arm and open-label studies.[59-61] At the time of the latest data cut-off dates presented within this submission, 200 paediatric and young adult patients with r/r B-cell ALL had received an infusion with tisagenlecleucel.[2, 5, 6] The key results from the final primary endpoint analysis (DCO 13th Apr 2018) and latest data cut-off (17th Nov 2022) from the ELIANA trial are summarised below:[2, 63]

- At the final primary endpoint analysis (DCO 13th Apr 2018), ORR within 3 months post-tisagenlecleucel infusion in 79 patients was 82.3% (95% CI: 72.1, 90.0).[12] The primary endpoint was previously met at the first interim analysis (DCO 17th Aug 2016) and at the data cut-off (31st Dec 2017)[68, 74]
- 98.5% patients with a BOR achieved MRD-negative disease, a reliable indicator of reduced risk of further relapses[12]

- Responses were also highly durable with median DoR of 46.8 months (95% CI: 17.8, NE) and median EFS of 23.7 months (95% CI: 9.2, NE).[2] The estimated probability of RFS and EFS at Month 60 were 49.2% (95% CI: 34.6, 62.3) and 41.8% (95% CI: 29.1, 53.9) respectively[2]
- Median OS was not reached after a median follow-up duration of 79.4 months between the first tisagenlecleucel infusion and LPLV. There were 33 OS events, with the estimated probability of survival being 88.6% (95% CI: 79.3, 93.9) at Month 6, 67.8% (95% CI: 56.1, 77.0) at Month 24 and 55.7% (95% CI: 43.6, 66.3) at Month 60[2]
- There were improvements in patient-reported outcomes as demonstrated by PedsQL and EQ-5D-3L scores. The mean change from baseline in the PedsQL total score were 14.8, 26.2 and 25.3 at Months 6, 24 and 60 respectively. Similarly, the mean change from baseline in the EQ VAS score were 16.9, 22.4 and 23.6 at Months 6, 24 and 60 respectively[2]

Results from the ENSIGN and B2101J trials supported the findings of the pivotal ELIANA trial. Together, results from all three trials indicate the depth and quality of response possible with tisagenlecleucel, with a meaningful and consistent benefit observed across all three trials.

These results are further corroborated by real-world treatment effectiveness of tisagenlecleucel during the managed access period as captured in the NHSE CDF report, which show even better OS results than the ELIANA, ENSIGN and B2101J trials: median OS was not reached.[2, 3, 5, 6] OS at 6 months was 90% (95% CI: 82, 94), 12 months OS was 81% (95% CI: 73, 88), OS at 18 months was 78% (95% CI: 68, 85), OS at 24 months was 72% (95% CI: 62, 80) and OS at 36 months was 67% (95% CI: 55, 77).[3]

The safety analysis conducted across all three trials indicate that tisagenlecleucel has a consistent and manageable safety profile. AEs primarily occurred within the first eight weeks post-tisagenlecleucel infusion, with CRS the most commonly reported AE across all trials occurring in 77.2%, 78.1% and 89.5% patients in ELIANA, ENSIGN and B2101J, respectively.[2, 5, 6] In almost all cases, development of CRS occurred between 1 to 10 days after infusion; no CRS events were reported after eight weeks post-infusion in both ELIANA and ENSIGN (not reported in B2101J), and no deaths were associated with CRS across all three trials.[2, 5, 6] Whilst patients may require admission to ICU and treatment with systemic anti-cytokine therapy, such as tocilizumab, treatment is manageable, and protocol guidelines are available. B-cell aplasia was also a common AE experienced across all three trials. Though no real-world evidence on B-cell aplasia rates in the UK clinical setting was found, the incidences of B-cell aplasia reported in the trials are not anticipated to differ greatly to UK clinical practice. B-cell aplasia can be managed effectively through appropriate treatment with immunoglobulin replacement therapy.

Comparative evidence of tisagenlecleucel versus the relevant comparators to this submission

Due to the single-arm nature of the clinical trials investigating tisagenlecleucel and the relevant comparators (identified above), the conduct of a conventional indirect treatment comparison was not possible. As such, the use of a MAIC approach was explored as part of a scenario analysis (see Section B.3.10.3)and full details of the methodology and results of this approach are presented in Appendix D. There are currently no clinical trials that provide clinical evidence for salvage chemotherapy, specifically FLAG-IDA, and therefore no MAIC was conducted specifically for tisagenlecleucel versus FLAG-IDA. Instead, the efficacy of clofarabine

monotherapy from the study by Jeha *et al.* (2006) were used as a proxy for the efficacy of FLAG-IDA, and a MAIC was conducted versus these data. Within the MAIC analysis, tisagenlecleucel was found to have superior OS compared to both blinatumomab and salvage chemotherapy (see Section B.2.9).

Strengths and limitations of the clinical evidence base

The clinical evidence presented for tisagenlecleucel has been identified through an SLR of clinical trials investigating the efficacy and safety of treatment options for paediatric and young adult patients with r/r B-cell ALL. The clinical evidence for the effectiveness of tisagenlecleucel is derived from three single-arm clinical trials (ELIANA, ENSIGN and B2101J), all of which were submitted as part of the Marketing Authorisation application to the EMA for this indication. The choice of a single arm study design for all three trials is supported by multiple factors. The absence of effective therapies in the patient population enrolled and the high unmet medical need in the enrolled patient population results in the lack of an appropriate comparator for a controlled trial. In addition, the extremely poor prognosis of r/r B-cell ALL patients means that enrolling in an RCT could be viewed as unethical. Furthermore, compelling results with tisagenlecleucel in a Phase I/IIA trial (B2101J) and the receipt of "Breakthrough Therapy" designation and fast track approval further supports the use of a single-arm design.[62, 101, 102]

The eligibility criteria of all three tisagenlecleucel clinical trials are well-matched to the decision problem outlined in the final scope for this appraisal. Although ENSIGN and B2101J were US trials, ELIANA was an international trial, which included EU sites such as Germany, Austria, Belgium and Spain. Thus, the ELIANA trial, which is used in the economic model, can be considered to provide evidence on the efficacy and safety of tisagenlecleucel in a patient population relevant to both the scope of this appraisal and to the expected patient population in clinical practice, as accepted by the ERG in the original appraisal (TA554).[9, 14] The availability of long-term follow-up data from the latest data cut-off of the ELIANA trial provides robust evidence on the curative potential of tisagenlecleucel, thereby addressing limitations of the ELIANA trial data raised in TA554. [9]

ORR was the primary outcome in ELIANA and ENSIGN, and was measured as part of the primary outcome in B2101J. This is considered a standard outcome measurement in ALL, and MRD-negative ORR correlates well with long-term outcomes for patients.[103, 104] Furthermore, the patient population treated with tisagenlecleucel is large, at 200 patients, particularly considering the rare nature of paediatric and young adult r/r B-cell ALL.

The key limitation of the evidence base is the lack of direct evidence identified for tisagenlecleucel versus relevant comparators to inform estimates of relative effect. In order to provide estimates of the relative effectiveness of tisagenlecleucel versus blinatumomab and salvage chemotherapy regimens, MAICs were conducted based on the individual patient-level data (IPD) from ELIANA and summary data from von Stackelberg *et al.* (2016) for blinatumomab and Jeha *et al.* (2006) for salvage chemotherapy (FLAG-IDA), based on the guidance provided in the NICE Decision Support Unit (DSU): Technical Support Document (TSD) 18.[105]

The von Stackelberg *et al.* (2016) study and Jeha *et al.* (2006) study were both used as comparator efficacy data sources for blinatumomab and salvage chemotherapy respectively in the original submission (TA554), noting the committee's acceptance of von Stackelberg *et al.* (2016). When compared to newly identified studies on the use of blinatumomab in the latest March 2023 SLR update (see Section B.2.9), the von Stackelberg *et al.* (2016) study remained

the most appropriate source of comparator efficacy data as it represents the pivotal clinical trial for blinatumomab in paediatric r/r B-cell ALL patients and due to the lack of new compelling data identified. Whilst the ERG noted a preference for Kuhlen *et al.* (2018) as the comparator efficacy data source for salvage chemotherapy in the original appraisal (TA554), Kuhlen *et al.* (2018) is limited in its comparability to the tisagenlecleucel trials given that all patients had received prior-SCT and approximately 20% of the patient population had extramedullary relapse. Comparison to newly identified studies in July 2019 SLR update (see Section B.2.9) found that Jeha *et al.* (2006) remained the most appropriate data source as the other studies had limited sample sizes and used chemotherapy regimens that were not reasonable proxies for FLAG-IDA.

The comparison of tisagenlecleucel with blinatumomab and salvage chemotherapy showed a consistent benefit in OS over time for both the naive comparison and MAIC performed. The OS benefit for tisagenlecleucel in the naïve comparison were statistically significant with a HR of 0.26 (95% CI: 0.16, 0.43) when compared to blinatumomab and 0.14 (95% CI: 0.09, 0.24) when compared to salvage chemotherapy. Similarly, the OS benefits for tisagenlecleucel in the MAIC were statistically significant with a HR of 0.31 (95% CI: 0.18, 0.55) when compared to blinatumomab and 0.19 (95% CI: 0.10, 0.35) when compared to salvage chemotherapy.

Conclusion

Tisagenlecleucel, a CAR-T, is a one-time potentially curative treatment which offers high rates of durable CRs and manageable safety profile. The availability of long-term follow-up tisagenlecleucel efficacy data and its relative efficacy to relevant comparator treatments strengthen the case for the provision of tisagenlecleucel as part of routine commissioning to ensure continued access to curative r/r B-cell ALL treatments for the patient population of interest in this submission.

B.3 Cost effectiveness

Summary of cost-effectiveness

- A *de novo* cost-effectiveness model was constructed in Microsoft Excel® for the original submission (TA554) to assess the cost-effectiveness of tisagenlecleucel compared to established clinical management in the UK, for the management of paediatric and adult patients aged up to 25 with r/r B-cell.[9] The cost-effectiveness model submitted as part of TA554 was considered to be appropriate for decision-making by the NICE committee and has been adapted for this submission.[1] The developed model was a cohort-based partitioned survival model (PSM) consisting of three mutually exclusive health states: (i) *event-free survival* (EFS), (ii) *relapsed/progressed disease* (PD), and (iii) *death*. The model structure also included a decision tree prior to entry into the PSM structure for the tisagenlecleucel arm only.
- Tisagenlecleucel was compared to blinatumomab using clinical efficacy data from the study by von Stackelberg *et al.* (2016) and salvage chemotherapy (FLAG-IDA) using clinical efficacy data from a clofarabine monotherapy study by Jeha *et al.* (2006) as a proxy.[7, 8] These sources of comparator efficacy data were also used in the original appraisal (TA554) and have been validated with clinical experts consulted as part of this appraisal.[4]
- It should be noted that given the establishment of tisagenlecleucel as a treatment option following its reimbursement via the CDF, there may be selection bias associated with the use of comparators in current clinical practice, particularly for those patients who are not good candidates for allo-SCT. The comparison of relevance in this submission is therefore, not between tisagenlecleucel and current use of comparators in clinical practice, but between tisagenlecleucel and the expected use of comparators if tisagenlecleucel were not available
- Given the curative potential of tisagenlecleucel, OS and EFS estimates were extrapolated using a mixture cure model approach. This approach was also used for both blinatumomab and salvage chemotherapy (FLAG-IDA), in line with the ERG preference in TA554[9]
- Utility values for event-free and relapsed/progressed disease states were derived from the study by Kelly *et al.* (2015)[106]
- Resource use and costs included in the model were based on information from the ELIANA trial, previous TAs, and appropriate published sources including the BNF, the eMIT and NHS reference costs 2021–2022
- Extensive feedback from several UK clinical experts who were experienced in the treatment of r/r B-cell ALL and had the clinical experience of using tisagenlecleucel was sought in order to validate assumptions and inputs included in the model

Base case cost-effectiveness results

- Tisagenlecleucel was found to be associated with higher costs but also higher life years gained and higher QALYs than both blinatumomab and salvage chemotherapy (FLAG-IDA)
- Under the base case assumptions, tisagenlecleucel (at list price) was associated with ICERs of [redacted] and [redacted] versus blinatumomab and salvage chemotherapy (FLAG-IDA). When provided with the simple confidential PAS discount ([redacted]), the ICERs were £19,218 and £30,778 respectively.
- When considering the severity of the r/r B-cell ALL, with the application of a x1.7 severity modifier, tisagenlecleucel (at list price) was associated with ICERs of [redacted] and [redacted] versus blinatumomab and salvage chemotherapy (FLAG-IDA). When provided with the simple confidential PAS discount ([redacted]) and the x1.7 severity modifier, the ICERs were £11,304 and £18,105 respectively; these ICERs are below the cost-effectiveness threshold of £30,000 per QALY. When considering tisagenlecleucel at PAS price and a cost-effectiveness threshold of £30,000 per QALY with the x1.7 severity modifier applied, the probability of tisagenlecleucel being cost-effective is 85% when compared to blinatumomab and 89% when compared to salvage chemotherapy.
- Given that tisagenlecleucel is an ATMP with curative potential, when a non-reference discount rate of 1.5% is applied, tisagenlecleucel (at list price) was associated with ICERs of [redacted] and [redacted] versus blinatumomab and salvage chemotherapy (FLAG-IDA). When provided with the

simple confidential PAS discount ([redacted]), the ICERs were £7,708 and £12,462 respectively.

Sensitivity analyses

- ICER estimates obtained from the probabilistic sensitivity analysis (PSA) to take account of combined uncertainty in the model were similar to the base case deterministic ICERs
- Of parameters explored in the deterministic sensitivity analysis (DSA), comparator treatment cost and EFS utility were found to be the most influential parameters on the ICERs against blinatumomab and salvage chemotherapy, respectively, with rates of subsequent allo-SCT the second most influential parameters in both comparisons
- Scenario analyses were conducted to explore the impact of alternative parametric mixture cure model distributions for OS, alternative efficacy inputs, costs, long-term assumptions and any additional scenarios. In all of the scenario analyses conducted, the ICERs for tisagenlecleucel at PAS price with the x1.7 severity modifier applied were found to be below a cost-effectiveness threshold of £30,000 per QALY

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify any previously published cost-effectiveness studies to support the development of a cost-effectiveness model for tisagenlecleucel as a treatment for patients aged up to 25 with r/r B-cell ALL. The searches were performed on 20th March 2023 and full details of the SLR search strategy, study selection process, results and quality assessment of the included studies are reported in Appendix G.

The SLR identified a total of 17 publications reporting on 16 unique studies. Cost-effectiveness studies conducted in a European setting were prioritised for extraction based on highest relevance to the current NICE submission. A summary of the nine publications reporting on eight unique studies prioritised for data extraction can be found in Table 30, with further details presented in Appendix G, including those cost-effectiveness studies in non-European settings identified but deprioritised for extraction.

A prior NICE single technology appraisal in r/r B-cell ALL, TA893 (brexucabtagene autoleucel), published after the SLR search date, was identified to be relevant to this appraisal and informed the NHS tariff in the economic model (see Section B.3.5.1).[58]

Table 30: Summary list of published cost-effectiveness studies

Study	Summary of model	Patient population (average age in years)	Incr. QALYs	Incr. Costs	ICER (cost per QALY)
Carey *et al.* (2022)[107, 108]	A cost-effectiveness study using short-term decision tree model and partitioned survival model with three health states and 88-year time horizon	Paediatric and young adult patients with R/R ALL	Tisagenlecleucel vs. blinatumomab: 2.15 vs. FLAG-IDA: NR	Tisagenlecleucel vs. blinatumomab: €156,928 vs. FLAG-IDA: NR	Tisagenlecleucel vs. blinatumomab: €73,086 vs. FLAG-IDA: €120,528
Thielen *et al.* (2020)[109]	A cost-effectiveness study using three-state partitioned survival model with lifetime time horizon	Paediatric patients with R/R ALL	Tisagenlecleucel vs. clofarabine monotherapy: 10.77 vs. clofarabine combination therapy: 9.56 vs. blinatumomab: 9.01	Tisagenlecleucel vs. clofarabine monotherapy: €391,876 vs. clofarabine combination therapy: €358,759 vs. blinatumomab: €285,420	Tisagenlecleucel vs. clofarabine monotherapy: €36,378 vs. clofarabine combination therapy: €37,531 vs. blinatumomab: €31,682
Maria *et al.* (2020)[110]	A cost-effectiveness and cost-utility study using three-state partitioned survival model with lifetime time horizon	Paediatric and young adult patients with R/R ALL	Tisagenlecleucel vs. salvage chemotherapy (FLAG-IDA): 8.97	Tisagenlecleucel vs. salvage chemotherapy (FLAG-IDA): €258,378.40	Tisagenlecleucel vs. salvage chemotherapy (FLAG-IDA): €28,818.52
SMC (2019)[111]	A cost-utility analysis using a cohort-based partitioned survival model with 88-year time horizon	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse	Tisagenlecleucel vs. blinatumomab: NR vs. salvage chemotherapy (FLAG-IDA): NR	Tisagenlecleucel vs. blinatumomab: NR vs. salvage chemotherapy (FLAG-IDA): NR	Tisagenlecleucel (with PAS) vs. blinatumomab: NR vs. salvage chemotherapy (FLAG-IDA): £25,238
HAS (2022)[112]	No details of model available	Children or adolescents aged 1 year or older with high-risk first	Blinatumomab vs. conventional consolidation chemotherapy: NR	Blinatumomab vs. conventional consolidation chemotherapy: NR	Blinatumomab vs. conventional consolidation chemotherapy: €7,392

		relapsed Ph(-) CD19 positive B precursor ALL			
Moradi-Lakeh *et al.* (2021)[113]	A cost-utility study using three-state partitioned survival model with lifetime time horizon	Paediatric and young adult patients up to 25 years of age with B-cell precursor ALL that is refractory or in second-line or later relapse, corresponding to the populations of ELIANA, ENSIGN, and B2101J trials	Tisagenlecleucel vs clofarabine combination: 6.65 vs. blinatumomab: 6.22 vs. salvage chemotherapy: 7.90	Total costs associated with intervention and comparators: Tisagenlecleucel: 511,939 CHF clofarabine combination: 282,388 CHF blinatumomab: 285,595 CHF salvage chemotherapy: 259,565 CHF	Tisagenlecleucel vs clofarabine combination: 34,530 CHF vs. blinatumomab: 36,419 CHF vs. salvage chemotherapy: 31,961 CHF
NoMA (2018)[114]	A cost-effectiveness study using three-state partitioned survival model with 88-year time horizon	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse	Tisagenlecleucel vs. CEC chemotherapy: 6.95 (mITT; Novartis); 3.67 (ITT; NoMA); 4.62 (mITT; NoMA)	Tisagenlecleucel vs. CEC chemotherapy: 2,826,440 NOK (mITT; Novartis); 2,391,847 NOK (ITT; NoMA); 2,993,564 NOK (mITT; NoMA)	Tisagenlecleucel vs. CEC chemotherapy: 406,605 NOK (mITT; Novartis); 651,101 NOK (ITT; NoMA); 648,088 NOK (mITT; NoMA)
Lis *et al.* (2012)[115]	A cost-effectiveness study using a decision-tree with lifetime time horizon	Children and adolescents with ALL who are relapsed or refractory, after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response, in the Polish setting	Clofarabine combination therapy vs. nelarabine: 2.66 vs. FLAG-IDA: 2.55	Clofarabine combination therapy vs. nelarabine: 86,715 PLN vs. FLAG-IDA: 77,356 PLN	Clofarabine combination therapy vs. Nelarabine: 27,529 PLN vs. FLAG-IDA: 26,046 PLN

Abbreviations: CEC: clofarabine, etoposide and cyclophosphamide; CER: cost-effectiveness ratio; CHF: Swiss francs; FLAG-IDA: fludarabine, cytarabine, idarubicin and G-CSF; G-CSF : granulocyte-stimulating colony factor; HAS: Haute Autorité de Santé; ICER: incremental cost-effectiveness ratio; mITT: modified intention-to-treat; NICE: National Institute for Health and Care Excellence; NOK: Norwegian Krone; NoMA: Norwegian Medicines Agency; NR: not reported; PAS, Patient Access Scheme; PLN: Polish Zloty; QALY: quality adjusted life year; SCT: stem cell transplant; SMC : Scottish Medicines Consortium.

B.3.2 *Economic analysis*

A *de novo* cost-effectiveness model was constructed in Microsoft Excel® for the original submission (TA554) to assess the cost-effectiveness of tisagenlecleucel compared to established clinical management in the UK, for the management of paediatric and adult patients aged up to 25 with r/r B-cell.[9] The cost-effectiveness model submitted as part of TA554 was considered to be appropriate for decision-making by the NICE committee and has been adapted for this submission.[1] In line with the NICE reference case, the economic analysis was conducted from the perspective of the NHS and personal social services (PSS), as described in the following sections.[116]

B.3.2.1 Patient population

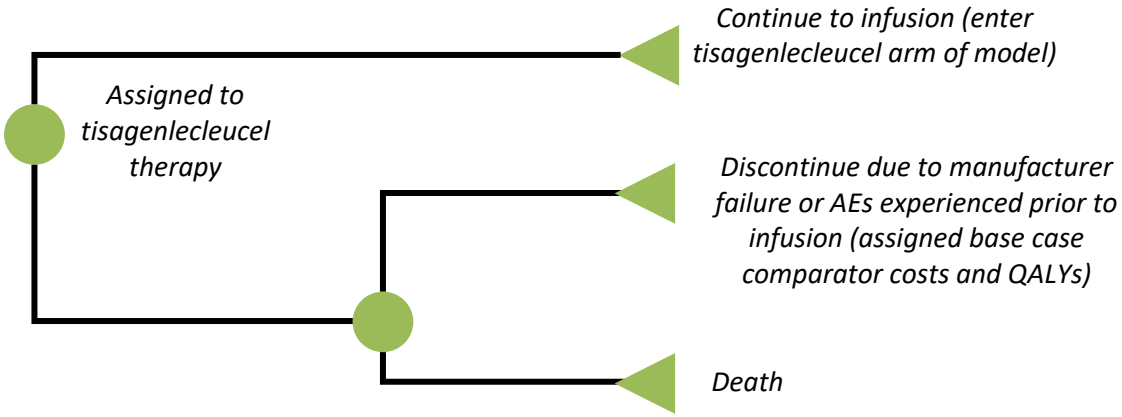
The patient population for the economic analysis comprised of patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-treatment or in second or late relapse. The patient population is in line with the licensed indication for tisagenlecleucel in r/r B-cell ALL (see Section B.1.1 and the decision problem addressed within this submission, as outlined in Table 2). The patient population is informed by the patient population evaluated in the pivotal tisagenlecleucel clinical trial in r/r B-cell ALL: ELIANA.[42]

B.3.2.2 Model structure

The developed model was a cohort-based partitioned survival model (PSM) consisting of three mutually exclusive health states: (i) *event-free survival* (EFS), (ii) *relapsed/progressed disease* (PD), and (iii) *death*. The health states considered by the model are in line with the outcomes most clinically relevant to the treatment of r/r B-cell ALL and are in line with previous economic evaluations submitted to NICE in r/r B-cell ALL in adults (TA450 and TA541), as well as the original submission for tisagenlecleucel in r/r B-cell ALL (TA554).[1, 11, 53] In addition to the PSM, the model structure included a decision tree prior to entry into the PSM structure for the tisagenlecleucel arm only. This decision tree element was included to capture the costs and benefits associated with patients who, in clinical practice, might be assigned for treatment with tisagenlecleucel and receive the costs of pre-treatment, but not ultimately receive tisagenlecleucel infusion. Non-infusion of some patients was seen in the tisagenlecleucel clinical trials and the potential for this is a feature of the unique manufacturing and administration process for tisagenlecleucel.[2] However, ongoing process improvements in tisagenlecleucel manufacturing have reduced the throughput time, thereby resulting in increased manufacturing capacity and an increased proportion of patients receiving tisagenlecleucel in clinical practice.[117]

The decision tree element of the model, applied to the tisagenlecleucel arm only, is presented in Figure 26.

Figure 26: Decision tree structure for tisagenlecleucel cohort



Abbreviations: QALYs: quality-adjusted life years.

Decision tree prior to PSM entry

The process of treatment with tisagenlecleucel is described in Table 3 of Section B.1.2. In summary, this consists of: (i) initial leukapheresis in hospital to obtain T-cells from the patient; (ii) cryopreservation of the extracted T-cells, shipping of these to a manufacturing facility and manufacturing of the anti-CD19 CAR-expressing T-cells; (iii) infusion of the CAR-T cells as a single-dose of tisagenlecleucel in hospital. Whilst the T-cells are being manufactured following leukapheresis, patients are administered bridging chemotherapy in order to stabilise their disease, as was done in the ELIANA, ENSIGN and B2101J trials.[59-61] In addition, the SmPC for tisagenlecleucel recommends that patients receive lymphodepleting chemotherapy prior to tisagenlecleucel infusion, to induce lymphopaenia and thus facilitate the engraftment and homeostatic expansion of tisagenlecleucel cells (see the SmPC in the reference pack).[10]

The pre-treatment process, from the decision to initiate the patient on tisagenlecleucel and arrange for the first step of leukapheresis, to the ultimate infusion with tisagenlecleucel, represents a period of time (and a process) during which there is the potential for events to occur that ultimately lead to the planned infusion of tisagenlecleucel not taking place. These potential events consist of a failure in the tisagenlecleucel manufacturing process, AEs leading to ineligibility for tisagenlecleucel infusion, or patient death. Patients who experience these events and are hence unable to receive infusion with tisagenlecleucel would experience outcomes and accrue costs that are different to those who do proceed to infusion. The decision tree model is therefore included within the economic model to capture this. As indicated in Figure 26:

- A proportion of patients (P_1) will successfully proceed to infusion with tisagenlecleucel. These patients therefore enter the PSM for tisagenlecleucel
- A proportion of patients (P_2) will not receive the tisagenlecleucel infusion, either due to failure in manufacture of the tisagenlecleucel product or due to experiencing an AE that renders them unsuitable to continue to tisagenlecleucel infusion. It is assumed that these patients would revert to treatment with the relevant comparator therapies to tisagenlecleucel. This is modelled by assigning the total (discounted) per patient quality-adjusted life years (QALYs) and costs associated with blinatumomab and salvage chemotherapy (FLAG-IDA) for this proportion of tisagenlecleucel patients. In line with the approach taken in the original submission, it was assumed that patients would equally revert to receive the relevant comparators in question (i.e. blinatumomab and salvage chemotherapy [FLAG-IDA]).[4] By employing this approach, there is an implicit assumption that the "failure event"

(manufacturer failure or AE) during the period whilst the patient is awaiting tisagenlecleucel infusion does not impact the outcomes that would have been achieved with the comparator had the patient been assigned to this comparator treatment initially.

- A proportion of patients (P_3) will not receive the tisagenlecleucel infusion due to death before the infusion is ready. These patients are associated with no further accrual of costs or QALYs beyond those assigned during the decision tree part of the model.

Details of the specific proportions of patients assigned to each arm of the decision tree and the costs and outcomes accrued for each arm over the decision tree are provided in Section B.3.5.

As the comparator therapies (blinatumomab and salvage chemotherapy [FLAG-IDA]) included within the economic analysis are not associated with the same process as described above for tisagenlecleucel, they are not associated with the potential of failure to proceed to infusion. As such, the decision tree is not required for the comparator arms of the model and is only a feature of the tisagenlecleucel arm of the model.

Partitioned survival model

The PSM comprises three mutually exclusive health states: (i) *EFS*, (ii) *PD*, and (iii) *death*. A cohort of paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse was modelled to enter the PSM in the EFS health state and to receive either tisagenlecleucel or a comparator therapy (salvage chemotherapy [FLAG-IDA] or blinatumomab). The proportion of patients in each heath state during each monthly model cycle was then determined for each therapy directly from the cumulative survival probabilities derived from the EFS and OS curves as follows:

- The proportion of patients occupying the EFS health state was calculated as the proportion alive and event-free (based on EFS curve)
- The proportion of patients occupying the PD state was calculated as the proportion alive (based on the OS curve) minus the proportion of patients alive and event-free (based on the EFS curve)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on the OS curve)

Patients were redistributed among the three health states at each model cycle.

The PSM structure was deemed appropriate to inform the cost-effectiveness of tisagenlecleucel for the following reasons. The partitioned survival approach allows for the modelling of OS and EFS based on study-observed events, which facilitates the replication of within-clinical trial data and means that the economic model is expected to accurately reflect disease progression and the observed survival profile of patients treated with tisagenlecleucel and the relevant comparator therapies. The model structure does not allow for patients to improve their health state, which reflects the progressive nature of the condition and is consistent with previous economic modelling in r/r B-cell ALL.[11, 53] The death health state is an absorbing health state.

Importantly, the EFS and OS curves can be constructed from summary Kaplan-Meier data in the absence of individual patient-level data (IPD). IPD were not available for comparators and the model therefore had to rely on published summary data, meaning this was an important benefit of this model structure. The model structure also captures time-dependency of underlying risks, thereby incorporating a cure element as characteristic of tisagenlecleucel curative profile. The

PSM structure also allows for uncertainty in survival explorations to be explored through scenario analyses with alternative distributions.

Finally, as noted above, the PSM structure has been used in previous economic models submitted to NICE in r/r B-cell ALL (TA450 and TA541) and has been accepted by the committee for the original submission for tisagenlecleucel for the treatment of r/r B-cell ALL (TA554).[1, 11, 53] The model has been revised in line with the committee preferences and ERG feedback during the initial appraisal (TA554); a summary of the model adaptations in this update submission is listed below in Table 32.

Features of the de novo analysis

OS and EFS data for tisagenlecleucel informing the economic model was derived from the pivotal tisagenlecleucel clinical trial, ELIANA.[2] Full details of the clinical efficacy sources for tisagenlecleucel and the relevant comparators are provided in Section B.3.3.2. Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Cost components considered within the economic analysis included: pre-treatment costs, treatment costs and associated outpatient administration costs, hospitalisation and intensive care unit (ICU) costs, AE costs, costs associated with subsequent allo-SCT, other medical costs, and terminal care costs. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of tisagenlecleucel versus each comparator was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the UK NHS and Personal Social Services (PSS) in England over a time horizon of 88 years. This was considered to represent a lifetime time horizon given the mean age of patients at the start of the model was 12 years, and was chosen to comprehensively capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of their treatment. A monthly cycle length was considered in the base case, and both costs and clinical outcomes were discounted at 3.5% annually.

Justification for consideration of non-reference case discounting of 1.5% annually

In addition to reference case discounting of 3.5% annually, a scenario analysis was conducted in which a non-reference case annual discount of 1.5% was applied to costs and clinical outcomes (see Section B.3.10.3)

As noted in the case for change consultation document for the NICE methods of health technology evaluation, "*NICE understands there is broad interest in potentially curative technologies including ATMPs, and a policy-level drive to support them*".[118] The report explored the use of a non-reference case discount of 1.5% for these technologies that have high upfront costs and long-term health benefits such as ATMPs and other one-off treatments. Following consultation, Section 4.5.3 of the manual states the "*committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects*" if certain criteria are met.[16] Table 31 contains further details of the criteria set out by NICE for applying a discount rate of 1.5% per year, demonstrating that these criteria are met.

Table 31: NICE criteria for applying 1.5% discount rate and justification

NICE criteria for applying non-reference case discount of 1.5%	Demonstration that NICE criteria is met in the population of interest
The technology is for people who would otherwise die or have a very severely impaired life	For patients with r/r B-cell ALL, prognosis is extremely poor, with median OS of 3–7.5 months following second or later relapse having been previously reported.[7, 8] Current treatment options are associated with poor remission rates, reduced HRQoL, as well as medical and psychosocial consequences.[21, 30, 31] As shown in Section B.3.6, this means that patients live severely shortened or impaired life, with expected quality-adjusted life expectancy estimated to be less than 24 months.
It is likely to restore them to full or near-full health.	The longest-term follow-up data for tisagenlecleucel from ELIANA demonstrate a plateau in OS for tisagenlecleucel after 24 months, with 55.7% (95% CI: 43.6%, 66.3%) of all patients with r/r B-cell ALL alive at 5 years. Furthermore, OS extrapolations based on the ELIANA long term follow-up data (see Section B.3.3.3) demonstrate 42.4% of patients achieving long-term survival. Clinically meaningful improvements in HRQoL were consistently observed, with mean change from Baseline in PedsQL greater than 4.4 at all timepoints (see Section B.2.6.2). Mean EQ-VAS scores at follow-up timepoints were also comparable to the normative means of the general population, demonstrating the potential of tisagenlecleucel to restore patients to full or near-full health (see Section B.2.6.2).
The benefits are likely to be sustained over a very long period.	In the ELIANA trial, median OS has not yet been reached, even after over 6 years median follow-up from tisagenlecleucel infusion. The plateau in OS that emerged at 24 months has been sustained as at the latest data cut-off of November 2022. In addition to clinical trial evidence, clinical experts experienced in the use of tisagenlecleucel since reimbursement via the CDF in 2018 have indicated that 40% of patients would be anticipated to be cured following treatment with tisagenlecleucel.

Abbreviations: CDF: Cancer Drugs Fund; HRQoL: health-related quality of life; NICE: National Institute of Health and Care Excellence; OS: overall survival; pALL: paediatric acute lymphoblastic lymphoma; r/r: relapsed or refractory.

A summary of the key features of the de novo economic analysis and their justification is provided in Table 32. Other than TA554, no previous appraisals have been conducted by NICE in patients up to 25 years of age with r/r B-cell ALL hence a comparison to the methodologies used in the blinatumomab and inotuzumab adult appraisals was made.

Table 32: Features of the economic analysis

Factor	Previous evaluations				Current evaluation (Update of tisagenlecleucel [TA554])	
	Blinatumomab (TA450)[53]	Inotuzumab ozogamicin (TA541)[11]	Tisagenlecleucel (TA554)[1]		Chosen values	Justification
			Company base-case	ERG-preferred		
Time horizon	Lifetime horizon (50 years)	Lifetime horizon (60 years)	Lifetime horizon (88 years)		Lifetime horizon (88 years)	In line with the NICE reference case[116]
Cycle length	Weekly	28 days	Monthly		Monthly	Considered sufficiently granular to accurately capture modelled costs and outcomes
Discount rate	3.5% for both costs and health benefits (1.5% for health outcomes in scenario analyses)	1.5% for both costs and health benefits (3.5% in scenario analyses)	3.5% for both costs and health benefits		3.5% for both costs and health benefits (1.5% for health outcomes in scenario analyses)	In line with the NICE reference case.[116] A non-reference case discount has been explored as part of a scenario analysis, as the criteria for this discount rate to apply (see Table 31 above)
Perspective	NHS/PSS in England	NHS/PSS in England	NHS/PSS in England		NHS/PSS in England	In line with the NICE reference case[116]
Cure effect?	A cure effect was assumed whereby after 5 years, surviving patients are considered long-term survivors who then follow general population mortality	A cure effect was assumed whereby after 3 years, surviving patients are considered long-term survivors who then follow general population mortality	• A cure effect was modelled via mixture cure parametric survival models. Non-cured patients follow parametric survival extrapolations reflecting disease-specific mortality, and cured patients follow general population mortality • The overall survival profile was bounded by general population mortality, adjusted with an SMR (9.05) based on literature value[119]		• A cure effect was modelled via mixture cure parametric survival models. Non-cured patients follow parametric survival extrapolations reflecting disease-specific mortality, and cured patients follow general population mortality	• The assumption of cure is in line with that previously accepted by NICE in the original submission (TA554)[9] • In TA554, the SMR adjustment to general population mortality was modelled as a multiplier of 9.05.[9] This value was considered to

					• The overall survival profile was bounded by general population mortality, adjusted with an SMR (4) based on clinical opinion	underestimate long-term survival of cured patients by clinical experts, and has therefore been amended to 4 to better reflect expected long-term survival
Clinical parameters	• Clinical parameters (response, EFS and OS) used in the economic model base case were derived from the TOWER RCT[57] • It was assumed that people who survived more than four years were cured	• Clinical parameters (PFS and OS) were derived from the INO-VATE 1022 RCT[120] • It was assumed that people who survived more than 36 months (three years) were cured	• Clinical parameters (EFS and OS) for tisagenlecleucel used in the economic model were derived from a pooled analysis of the ELIANA, ENSIGN and B2101J clinical trials[59-61] • For blinatumomab, salvage chemotherapy comparators, the sources of clinical parameters were von Stackelberg *et al.* (2016), Jeha *et al.* (2006) • A mixture cure model approach was used for tisagenlecleucel and blinatumomab. Mixture cure models for salvage chemotherapy were implausible; therefore a standard parametric model was used with an assumption that people surviving more	• The ERG highlighted the short follow-up period for tisagenlecleucel, thereby adding uncertainty to the extrapolation of OS data for tisagenlecleucel[9] • For blinatumomab, the ERG were in agreement with the use of von Stackelberg *et al.* (2016) study as a comparator efficacy data source given that it was the only relevant trial evaluating blinatumomab in paediatric patients • For salvage chemotherapy, the ERG preferred the use of Kuhlen *et al.* (2017) as an efficacy data source for FLAG-IDA due to its longer follow-up duration and larger	• Clinical parameters (EFS and OS) for tisagenlecleucel used in the economic model were derived from ELIANA only[2] • For blinatumomab and salvage chemotherapy comparators, the sources of clinical parameters were von Stackelberg *et al.* (2016) and Jeha *et al.* (2006), respectively. • A mixture cure model approach was used for tisagenlecleucel, blinatumomab and salvage chemotherapy	• Given the differences between ELIANA, ENSIGN and B2101J clinical trials and the availability of long-term follow-up data from the ELIANA trial, data derived from the ELIANA trial was considered the most appropriate source of efficacy data • Following a clinical SLR conducted in March 2023 (see Section B.2.9) to identify new clinical trial evidence for comparators in question, von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) were considered the most appropriate sources of comparator efficacy data. The von Stackelberg *et al.* (2016) study was accepted as an

			than 60 months (five years) were cured	sample size • However, the company raised concerns on the appropriateness of using Kuhlen *et al.* (2016) as a data source given the higher rate of SCTs received in the trial population compared to the UK patient population and potential overestimation of OS. Therefore, the company deemed the Jeha *et al.* (2006) study as a more appropriate source of salvage-chemotherapy efficacy data.[9] • ERG preferred the use of mixture-cure model for salvage chemotherapy to retain consistency with the model approaches used for the other interventions and more clinically plausible results[9] • However, based on the UK clinical validation exercise held as part of the original appraisal, the use of mixture-		appropriate comparator efficacy data source by the ERG in TA554.[9] This was further validated by UK clinical experts consulted as part of this updated submission, and considered as the most appropriate source of comparator efficacy data given its long-term follow-up and inclusion of paediatric data[4] • No new studies were identified for FLAG-IDA in the latest SLR update and therefore, Jeha *et al.* (2006) was considered to be the most appropriate comparator efficacy data source for salvage chemotherapy, in line with the approach taken for the original submission (TA554) • A mixture cure model approach was used for consistency across all interventions and comparators, aligned to the ERG's preference in TA554[9]

				cure model for salvage chemotherapy were not considered appropriate given that cure fractions and long-term survival extrapolations were too optimistic[14]		

Source of utilities	NR	• Baseline (pre-treatment) utility values and post-treatment with and without response health state utilities were informed by the INO-VATE 1022 RCT[120]
		• Post-HSCT utilities were derived from Kurosawa *et al.* (2016)
		• Progression health state utilities were taken from the study by Aristides et al. (2015)
			• Kelly *et al.* (2015)[106]:
			  • EFS: 0.91
			  • PD: 0.75
				• ERG preferred the use of trial-derived utilities for patients in EFS (i.e. 0.80) and PD (i.e. 0.63) up to two years as this data would incorporate disutilities associated with treatment and longer-term AEs	• Kelly *et al.* (2015):[106]
					  • EFS: 0.91
					  • PD: 0.75
						• In line with the original appraisal of r/r B-cell ALL (TA554), utility values were derived from Kelly *et al.* (2015) and was accepted by the committee.[9, 106] This study was used as the source of utility values in the NICE mock appraisal of regenerative therapies[39]
						• Despite limited sample sizes, a scenario which incorporates EQ-5D utility values from the ELIANA trial has also been explored in this submission, in line with the ERG preference in TA554 (see Section B.3.10.3)[9, 106]

Source of costs	• NHS Reference Costs • PSSRU	• NHS Reference Costs	• NHS Reference Costs • PSSRU • BNF/eMIT		• NHS Reference Costs • PSSRU	NHS Reference Costs, PSSRU, BNF and eMIT are standard sources of UK-relevant costs and

	• BNF/eMIT	• PSSRU • BNF/eMIT			• BNF/eMIT • NHS CAR-T tariff	were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature. In the base case analysis, costs associated with the delivery of treatment with tisagenlecleucel were aligned to the NHS tariff accepted by the committee in TA893[58]
Resource use	Disease management costs (including hospitalisation and follow-up associated costs)	Disease monitoring costs (assumed to be captured in drug administration and AE costs)	Disease management costs (including pre-treatment, hospitalisation and follow-up associated costs). Rates were informed by clinical expert opinion and the ELIANA trial	ERG considered the resource use inputs appropriate but suggested for the inclusion of cost of G-CSF for adults receiving salvage therapy	Disease management costs (including pre-treatment, hospitalisation and follow-up associated costs). Rates were informed by clinical expert opinion and the ELIANA trial	Resource use inputs informing the model have been aligned with that of previous relevant evaluations and data collected form the ELIANA trial
Measure of health effects	QALYs	QALYs	QALYs	QALYs	QALYs	In line with the NICE reference case[116]

Abbreviations: BNF: British National Formulary; DLBCL: diffuse large B-cell lymphoma; eMIT: electronic Market Information Tool; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; QALY: quality adjusted life year; SF-36: Short Form Health Survey; SMR: standardised mortality ratio; TSD: Technical Support Document.
Source: Kelly *et al.* (2015);[106] eMIT;[121] NHS Reference Costs 2021-2022;[122] BNF;[123] TA450;[53] TA541;[11] TA893.[58]

B.3.2.3 Intervention technology and comparators

Intervention

The intervention considered in the analysis is tisagenlecleucel. Tisagenlecleucel is incorporated into the economic evaluation according to its marketing authorisation and in line with the decision problem described in Section B.1.1.

As described in Section B.1.2, tisagenlecleucel is an autologous anti-CD19 CAR T-cell therapy that recognises and eliminates all CD19 expressing target cells, including B-cell malignancies. It is provided as a single, one-time treatment for IV use only, at a dose of 0.6 to 6 x 10^8 CAR positive viable T cells (non-weight based). Patients must be treated with a lymphodepleting conditioning chemotherapy consisting of fludarabine (25 mg/m^2 IV daily for 3 days) and cyclophosphamide (250 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine). The efficacy evidence informing the tisagenlecleucel arm is derived from the tisagenlecleucel-infused population (n=79) from ELIANA.[2]

Comparators

As discussed in Section B.1.3, there is no established standard of care for patients with r/r B-cell ALL. At this stage in the pathway, treatment decisions are made on a case-by-case basis considering factors such as patient fitness, treatment goals, response and durability of response to prior therapy. It should also be highlighted that the comparison of relevance in this submission is not between tisagenlecleucel and current use of comparators in clinical practice, but between tisagenlecleucel and the expected use of comparators if tisagenlecleucel were not available. Comparators considered in the analysis are blinatumomab and salvage chemotherapy with respective dosing regimen details listed below.

Blinatumomab

The dose of blinatumomab incorporated into the economic model for patients up to the age of 18 was based on the dosing schedule used in the study by von Stackelberg *et al.* (2016):[7]

- Cycle 1 (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–7: 5 µg/m^2/day
    - Days 8–28: 15 µg/m^2/day
- Cycle 2 (4 weeks):
    - Days 1–28: 15 µg/m^2/day

It is acknowledged that patients over the age of 18 years would receive a higher adult dose of blinatumomab in clinical practice and therefore the adjusted dosing for adults was incorporated into the economic model for the proportion of patients estimated to be over the age of 18 (and under the age of 25) with r/r B-cell ALL based on population calculation estimates (8.3%; see the BIA template).

The dose of blinatumomab for patients over the age of 18 was based on the blinatumomab SmPC.[55]

- Cycle 1 (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–7: 9 µg/m^2/day

- Days 8–28: 28 µg/m^2/day

- Cycle 2 (4 weeks):
  - Days 1–28: 28 µg/m^2/day

Salvage chemotherapy (FLAG-IDA)

Clinical feedback received from UK clinical experts consulted as part of this submission indicated that only a minority of patients are treated with salvage chemotherapy with the majority of patients receiving blinatumomab following second relapse or relapse post-transplant.[4] However, salvage chemotherapy has been presented as part of this submission and considered as a relevant comparator for completeness. Feedback from UK clinical experts was that if they were to use salvage chemotherapy for 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 chemotherapy regimen of choice would be FLAG-IDA (fludarabine, cytarabine, G-CSF and idarubicin).[4] As such, the costs of salvage chemotherapy within the model were based on the drug acquisition and administration costs associated with treatment with the FLAG-IDA regimen.

The dosing regimen of FLAG-IDA was based on a protocol from the NHS Network Site Specific Group and validated with UK clinical experts and comprised 1 cycle of the following:[14, 124]

- Fludarabine 30 mg/m^2 daily for 5 doses
- Cytarabine 2 g/m^2 daily for 5 doses
- G-CSF 5 µg/kg daily for 12 doses
- Idarubicin 8 mg/m^2 daily for 3 doses.

Subsequent therapies

The economic analysis assumed that patients could receive a subsequent allo-SCT after initial treatment. No other subsequent therapies were considered as feedback from UK clinical experts was that following a further relapse in this setting, patients would be unlikely to receive further active therapy and any treatment would be palliative in nature. The rates of subsequent allo-SCT were obtained from the same clinical source used for the efficacy inputs in the base case analysis and are presented in Table 33.

It should be noted that, compared with those reported in the selected efficacy sources, clinical experts consulted as part of this submission estimated higher rates of allo-SCT following blinatumomab and salvage chemotherapy, which would be associated with higher subsequent treatment costs if included in the economic model. Clinicians' averaged estimates of the most likely value of subsequent SCT rates for blinatumomab in UK clinical practice were 56.7% (lowest plausible to highest plausible range: 25.0–73.3%) and 38.3% for salvage chemotherapy (lowest plausible to highest plausible range: 11.7–60.0%). This compares to subsequent SCT rates of 34.29% reported for blinatumomab in von Stackelberg *et al.* (2016),[7] and 14.75% reported for salvage chemotherapy in Jeha *et al.* (2006) (see Table 33).[8] In contrast, clinical experts estimated similar rates of allo-SCT following tisagenlecleucel (clinicians' averaged estimates: most likely value of 25.0% [lowest plausible to highest plausible: 11.7–50.0%]) to those observed in the ELIANA trial (22.78%).[2, 4]

However, this feedback should be interpreted with caution for several reasons:

- There may be selection bias associated with the use of comparators in current clinical practice resulting from the introduction of tisagenlecleucel, which has already become an established treatment option (reimbursed via the CDF):
    - Clinician feedback indicated that eligibility for subsequent SCT is a very important factor in clinical decision-making. Patients who are not good candidates for allo-SCT, such as those who have relapsed following prior allo-SCT (estimated to be approximately 50% of patients considered for tisagenlecleucel) or those who are chemo-refractory, are likely to be strong candidates for treatment with tisagenlecleucel. In contrast, comparator treatments such as blinatumomab are primarily used with the aim of achieving CR to bridge to subsequent allo-SCT (as discussed in Section B.1.3.2).[4]
    - Recent clinical experience of comparator therapies, and thus the resulting clinical expectations around predicted allo-SCT rates, may therefore not reflect the full population of relevance for this appraisal which includes patients that are not suitable for subsequent allo-SCT. As a result, it is likely that patients selected for treatment with comparator therapies in current clinical practice have a higher probability of achieving CR and proceeding to allo-SCT, compared with a world where tisagenlecleucel is not available. The comparison of relevance in this submission is not between tisagenlecleucel and current use of comparators in clinical practice, but between tisagenlecleucel and the expected use of comparators if tisagenlecleucel were not available.
- Clinical expert feedback initially estimated higher allo-SCT rates than CR rates for the same treatments, despite CR generally being considered a prerequisite for subsequent allo-SCT, with strict MRD negativity criteria required for patients to receive allo-SCT following blinatumomab. It is therefore possible that some clinician estimates for rates of allo-SCT following blinatumomab and salvage chemotherapy represent those receiving allo-SCT as a proportion of those patients who *previously achieved CR* on these treatments, not the proportion of treated patients.[4]

Given the uncertainty in these estimates, and in order to ensure fair comparisons between tisagenlecleucel and comparators, rates of subsequent allo-SCT were obtained from the clinical sources used for the efficacy inputs. These may better reflect clinical practice prior to the introduction of tisagenlecleucel as well as the expected subsequent allo-SCT rates for comparators when considered in the full population eligible for tisagenlecleucel in clinical practice.

A scenario based on real-world use of tisagenlecleucel during the managed access period is also explored.[3] In this scenario 12% of patients would be expected to receive a subsequent SCT.[3]

The costs associated with patients receiving a subsequent allo-SCT included in the model are described in Section B.3.5.1.

Table 33: Proportion of patients receiving subsequent allo-SCT in the model

Intervention	Rate of subsequent allo-SCT	Source
Tisagenlecleucel	22.78%	ELIANA CSR (DCO 17th Nov 2022)[2]
Salvage chemotherapy (FLAG-IDA)	14.75%	Jeha *et al.* (2006)[8]
Blinatumomab	34.29%	von Stackelberg *et al.* (2016)[7]

Abbreviations: allo-SCT: allogeneic haematopoietic stem cell transplantation; FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The patient baseline characteristics for the modelled cohort are provided in Table 34 and were based on the baseline characteristics of patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=79) in ELIANA (DCO 17th Nov 2022).[2]

As discussed in Section B.2.8 and Section B.2.12, given the differences in the patient baseline characteristics of the three tisagenlecleucel trials and that data with long-term follow-up from the ELIANA trial are now available, the ELIANA trial informed the economic model in this submission. The ELIANA trial is the pivotal trial that informed marketing authorisation for tisagenlecleucel in the indication of interest, has the longest follow-up and is most generalisable to the intended patient population and use of tisagenlecleucel in UK clinical practice.

The mean age and percentage of females in the cohort were used alongside England and Wales life tables (2018–2020) to calculate the natural mortality of the general population (see survival inputs and assumptions in Section B.3.3.3). The average body surface area (BSA) and weight were used to calculate drug acquisition costs where dosage was based on patient BSA or weight.

Table 34: Patient baseline characteristics of the base case economic analysis

Model parameter	Value	Source
Mean age	12 years	ELIANA CSR (17th Nov 2022)[2]
Percentage female	43.04%	
Average BSA[a]	1.25 m^2	
Average body weight	41.52 kg	

[a]Average BSA was calculated using the Mostellar formula from IPD.
Abbreviations: BSA: body surface area; IPD: individual patient data.
Source: ELIANA CSR (17th Nov 2022).[2]

B.3.3.2 Clinical efficacy inputs

Tisagenlecleucel

The primary efficacy outcomes considered within the economic model were OS and EFS. Consistent with the patient baseline characteristics of the modelled patient cohort, OS and EFS inputs for tisagenlecleucel were based on the patients who received tisagenlecleucel in ELIANA (DCO 17th Nov 2022).[2]

Comparators

As ELIANA was designed as a single-arm trial due to the nature of the rare disease and ethical considerations, published data for the comparators in a patient population comparable to the target population were used to inform the OS and EFS inputs for salvage chemotherapy (FLAG-IDA) and blinatumomab.

Blinatumomab

An SLR was conducted to identify relevant published data for the comparators in paediatric patients with r/r B-cell ALL. As described in Section B.2.9, the SLR identified three published studies of blinatumomab in paediatric patients aged up to 18 years with r/r B-cell ALL: a phase I/II open-label, multicentre, non-randomised study (n=70) published by Gore *et al.* (2018), a single-arm expanded open-access study (n=110) published by Locatelli *et al.* (2022) which is an extension of the RIALTO study, previously identified in the original SLR conducted for TA554 and a phase II clinical trial (n=70) published by von Stackelberg *et al.* (2016).[90]

For the base case analysis, OS data for blinatumomab were derived from von Stackelberg *et al.* (2016), the pivotal clinical trial for blinatumomab in paediatric patients with r/r/ B-cell ALL.[7] The eligibility criteria of the RIALTO study permitted patients previously treated with blinatumomab, and therefore it was considered that some patients may have overlapped between the von Stackelberg *et al.* (2016) and RIALTO studies. For this reason, it was not considered appropriate to explore a pooling of the von Stackelberg *et al.* (2016) and RIALTO studies.[7] The Gore *et al.* (2018) study reports on the same pivotal clinical trial as that reported by von Stackelberg *et al.* (2016), but data are only reported by allo-SCT use before or after blinatumomab and thus are not comparable to the full tisagenlecleucel trial populations.[7, 90] The OS data from von Stackelberg *et al.* (2016) alone were therefore used in the base case analysis. The committee in the original submission for tisagenlecleucel noted limitations associated with modelling blinatumomab using von Stackelberg *et al.* (2016), but considered its use appropriate for decision-making. The outcomes predicted by the von Stackelberg *et al.* (2016) study have been further validated with UK clinicians as part of this appraisal, who considered these to be representative of observed survival with blinatumomab in UK clinical practice.[4]

Salvage chemotherapy (FLAG-IDA)

As described in Section B.2.9, no published studies were identified in the SLR in the patient population of interest for salvage chemotherapy (specifically FLAG-IDA). As such, in order to model the efficacy of salvage chemotherapy (FLAG-IDA), OS data from a study of clofarabine monotherapy published by Jeha *et al.* (2006) were used as a proxy, in line with the approach taken in TA554.[8] The same efficacy source was also used in the NICE mock appraisal for regenerative therapies.[125] This assumption was validated by four UK clinical experts as part of the original appraisal, who were presented with the survival outcomes observed with clofarabine monotherapy in the Jeha *et al.* (2006) clinical trial and stated that they could be considered comparable to the survival outcomes that patients might achieve with salvage chemotherapy (FLAG-IDA) in UK clinical practice.[14]

In the original appraisal, the ERG highlighted a number of limitations associated with the Jeha *et al.* (2006) study, preferring a more recent study by Kuhlen *et al.* (2017).[9] However, the NICE committee acknowledged limitations with this study as a source of comparator efficacy data, including a higher proportion of patients in first relapse and the inclusion of patients with extramedullary relapse, and thus its potential to overestimate OS for salvage chemotherapy

(FLAG-IDA) in clinical practice. Therefore, Jeha *et al.* (2006) was used as comparator data source for salvage chemotherapy in this submission as well. However, as described in B.3.3.3, mixture-cure models were explored to reflect the curative potential of patients receiving allo-SCT following salvage chemotherapy and subsequent long-term survival predictions were validated by clinical experts as part of this appraisal.

Adjustment for patient characteristics

Given the single-arm nature of the clinical trials informing the efficacy inputs for tisagenlecleucel, blinatumomab and salvage chemotherapy, the trials were considered in terms of the similarity of their trial patient populations. Some differences between trial populations were identified for blinatumomab and salvage chemotherapy during the clinical validation previously performed as part of the original submission (TA554), though clinical experts indicated that it would be difficult to draw any conclusions as to the likely direction of any bias introduced by differences in the patient populations.[1, 14] As noted in Section B.2.9, a MAIC was conducted in order to explore adjustments of the ELIANA patient population to more closely match that of the von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) populations, respectively, and hence account for any impact of population differences on OS estimates.[7, 8] Ultimately, the MAICs found that the resulting changes to the tisagenlecleucel OS profile were modest in nature. The 95% confidence intervals of the adjusted ('matched') tisagenlecleucel curves were found to overlap considerably with the 95% confidence intervals of the unadjusted ('unmatched') tisagenlecleucel curves for OS versus both comparators, indicating that differences between matched and unmatched curves might simply represent uncertainty inherent in the sample estimates rather than a true difference in efficacy (see Figure 24 and Figure 25 in Section B.2.9). As such, it was considered more appropriate to preserve patient numbers and use the unadjusted OS profiles for tisagenlecleucel in the base case economic analysis.

B.3.3.3 Survival inputs and assumptions

As described in Section B.3.2.2, the proportion of patients in the EFS, PD and death health states at each cycle in the model were defined by OS and EFS curves.

As the follow-up periods for the relevant studies (ELIANA for tisagenlecleucel; Jeha *et al.* (2006) for salvage chemotherapy (FLAG-IDA) and von Stackelberg *et al.* (2016) for blinatumomab; see Sections B.2.6 and B.3.3.2) were shorter than the model time horizon, extrapolation from the observed OS and EFS data was required.[2, 7, 8]

In accordance with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored for extrapolation.[126] The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were then estimated for each parametric function.

In addition to these approaches, the fitting of mixture cure models was also explored. As reflected by NICE DSU TSD 21, it is well-established that standard parametric survival models are limited in their use for modelling hazard functions that follow more complex patterns.[127, 128] Therefore, in cases where there is evidence that the hazard function of an intervention has important changes over time that cannot be reflected by standard parametric distributions, it is necessary to explore other approaches. Flexible parametric models such as spline models represent one tool that can potentially be used to characterise more complex hazard functions. However, whilst these models may be found to produce a strong statistical fit to observed Kaplan-Meier data, they may produce

clinically unrealistic extrapolations in the long-term as they represent a purely statistical exercise in model fitting rather than an attempt to reflect the clinical mechanisms underlying the observed hazard function.[127, 129] As such, flexible parametric models were not explored for extrapolation.

Mixture cure models represent another approach to the modelling of survival with cancer therapies that can potentially account for more complex hazard functions in a manner that also reflects an underlying clinical process. Such models can be used where there is evidence to support that a proportion of the population treated with the intervention can be considered to be 'cured' (the 'cure fraction'). The cure fraction can be interpreted as a proportion of the population that would only be subject to background mortality (i.e. natural mortality of general population). This is reflected in the parameterisation of the mixture cure model, which models the population as a mixture of two subpopulations: one representing cured patients (the cure fraction), who have general population mortality, and one representing non-cured patients, who have a disease-related risk of death as defined by a parametric survival model. All mortality rates used in the model were bound by standardised mortality ratio (SMR)-adjusted age- and gender-specific natural mortality of the general population as a minimum.

The appropriateness of exploring mixture cure models to model the existence of a subpopulation of patients who are at the same risk of death as the general population (i.e. a cure fraction) in the context of this appraisal is also further supported by a number of observations.

- Firstly, the OS data from the latest data-cut-off of the pivotal ELIANA trial (17th Nov 2022), presented in Section B.2.6.2, is associated with a plateau from approximately 24 months, which is maintained until the end of the trial follow-up (79.4 months), representing a clear feature of the hazard function over time and strongly supporting a proportion of patients having long-term survival. The observation of a plateau in the OS profile is not unexpected clinically, as it is consistent with the expectations of the mechanism of action of tisagenlecleucel offering a cure, As outlined in Section B.1.2, by using the patients' own T-cells and their capacity for memory and surveillance, tisagenlecleucel acts as a 'living drug' that can provide an enduring response potentially over the course of a lifetime. It is also supported on a mechanistic level by the observation of a similar long-term plateau in the EFS data for tisagenlecleucel in the latest ELIANA data cut, which supports the notion that the plateau in the OS curve is not an artefact of the data but reflects that a proportion of patients remain relapse-free following treatment with tisagenlecleucel.
- Furthermore, in previous NICE appraisals of CAR T-cell therapies, a cure fraction was deemed appropriate to better reflect long-term survival expectations for patients following CAR-T infusion.[130, 131] Clinical experts also confirmed that it is reasonable to assume that a proportion of patients with r/r ALL who are treated with CAR T-cell therapy may have mortality hazards that behave more in line with the general population, estimating the most likely value for this cure fraction to be 40% (with lower and upper plausible limits of this proportion estimated to be 25–57%).[4]
- Outside of the considerations of the curative mechanism of action of tisagenlecleucel, the notion that a proportion of r/r B-cell ALL patients can achieve a cure has been established previously. In the NICE appraisal of blinatumomab in adult patients with r/r B-cell ALL, the manufacturer of blinatumomab assumed that patients still alive at 48 months could be assumed to be cured, citing UK clinical expert feedback in support of this assumption.[53] Although there was some discussion in this appraisal as to the exact timepoint at which this assumption could be applied, the concept itself was fully accepted. In their exploratory analysis of CAR-T as part of the NICE mock appraisal of regenerative therapies, the York group

adopted a similar assumption, modelling those patients still alive at year 5 of the analysis to be long-term survivors of ALL and "effectively 'cured'". These patients were associated with a mortality risk after 5 years based on general population age- and gender-adjusted all-cause risks of mortality adjusted for excess morbidity and mortality reported in cohorts of long-term survivors of ALL.[39] Feedback from UK clinical experts experienced in the treatment of r/r B-cell ALL in the paediatric and young adult setting was sought as part of the original appraisal (TA554), and the feedback supported the assumption that patients alive in the mid-term could be essentially assumed to be 'cured'; the timepoint at which this assumption could be made varied amongst expert feedback from 2 years to 5 years.[14]

For the parameterisation of the mixture cure models, the cure fraction was estimated based on a logistic regression, with the survival of these patients considered to follow the SMR-adjusted general population mortality as per the England and Wales life tables (2018–2020) in the cost-effectiveness model.[132] The survival of patients who were not cured was estimated using the standard parametric survival distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma). Overall statistical fit of the mixture cure models was evaluated through the use of the AIC and BIC, as for the standard parametric survival models.

Standard parametric survival models and mixture cure models were explored for all modelled treatments. In the absence of IPD for the comparator trials, pseudo-IPD were generated using the algorithm described by Guyot *et al.* (2012) based on available Kaplan-Meier plots and event information.[133] In determining the choice of survival model for the base case for each therapy, consideration was given to the following, as per the recommendations provided in NICE DSU TSD 14:[126]

- **AIC/BIC tests:** the AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the selected model
- **Graphical assessment of fit:** the visual inspection can evaluate how well a parametric survival model fits with the observed Kaplan–Meier curves. The parametric survival model that most closely follows the Kaplan–Meier curve could be considered the best fit
- **Clinical validation of short- and long-term extrapolations**

Feedback was obtained from three UK clinical experts (existing or former NHS Consultant Haematologists), all experienced in the treatment of r/r B-cell ALL and with clinical experience of using tisagenlecleucel, through pre-read questionnaire and subsequent discussions via teleconference.

In the pre-read questionnaire, in order to comprehensively validate survival extrapolations for tisagenlecleucel based on the latest data-cut of the ELIANA trial (DCO 17th Nov 2022), clinicians were first asked to provide lower, upper and most likely estimates for the proportion of patients they would expect to be event-free and alive at 1, 2, 5, 10 and 20 years on tisagenlecleucel. Clinical experts were provided with the latest Kaplan–Meier survival data from ELIANA as context to inform their estimates. In the subsequent teleconference, the clinical experts were then shown figures displaying the Kaplan–Meier data and the parametric survival models generated from these data. Survival estimates predicted by these models at various timepoints were also provided, as well as predicted cure fractions for the mixture cure models. Clinical experts were asked to indicate any extrapolations that they considered to be clinically implausible, as well as those that were preferred. Clinicians were also asked to provide lower, upper and a most likely estimate for the

proportion of patients who would achieve a cure fraction for patients receiving tisagenlecleucel and all comparators.

Using the results of the pre-read questionnaire and teleconference calls with the clinicians, candidate distributions that were deemed potentially clinically plausible were considered to model survival extrapolations for each treatment option. Clinically plausible distributions were those that did not predict survival above or below the upper and lower values elicited from the experts and were preferred by the experts. There was broad consistency between the individual assessments provided by the experts and between the different methods used to assess the plausibility of the various models.

It should be noted that clinical experts consulted as part of this submission estimated higher rates of allo-SCT following blinatumomab and salvage chemotherapy compared with those reported in the selected efficacy sources. As discussed in detail in Section B.3.2.3, this may be due to selection bias associated with the use of comparators in current clinical practice resulting from the introduction of tisagenlecleucel, which has already become an established treatment option (reimbursed via the CDF) particularly for those patients who are not good candidates for allo-SCT. In contrast, comparator treatments such as blinatumomab are primarily used with the aim of achieving CR to bridge to subsequent allo-SCT.[4] There may be some uncertainty in the patient population for which these allo-SCT rates were estimated. Therefore, clinical expectations around predicted survival and cure for patients treated with comparator treatments may not reflect the full population of relevance for this appraisal, which includes patients that are not suitable for subsequent allo-SCT, and may be biased in favour of comparator treatments. The comparison of relevance in this submission is not between tisagenlecleucel and current use of comparators in clinical practice, but between tisagenlecleucel and the expected use of comparators if tisagenlecleucel were not available.

Logical inconsistencies

To ensure that OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by SMR-adjusted age- and gender-specific natural mortality of the general population as a minimum (calculated using England and Wales life tables [2018–2020]). In addition, adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of patients alive being less than the proportion of patients alive and progression-free, could not occur (i.e. EFS was bound by OS as a minimum).

Overall survival

Tisagenlecleucel

For tisagenlecleucel, the OS IPD was used from ELIANA (DCO 17th Nov 2022).[2]

The AIC and BIC values for the various standard parametric models that were explored for the extrapolation of the OS data for tisagenlecleucel are summarised in

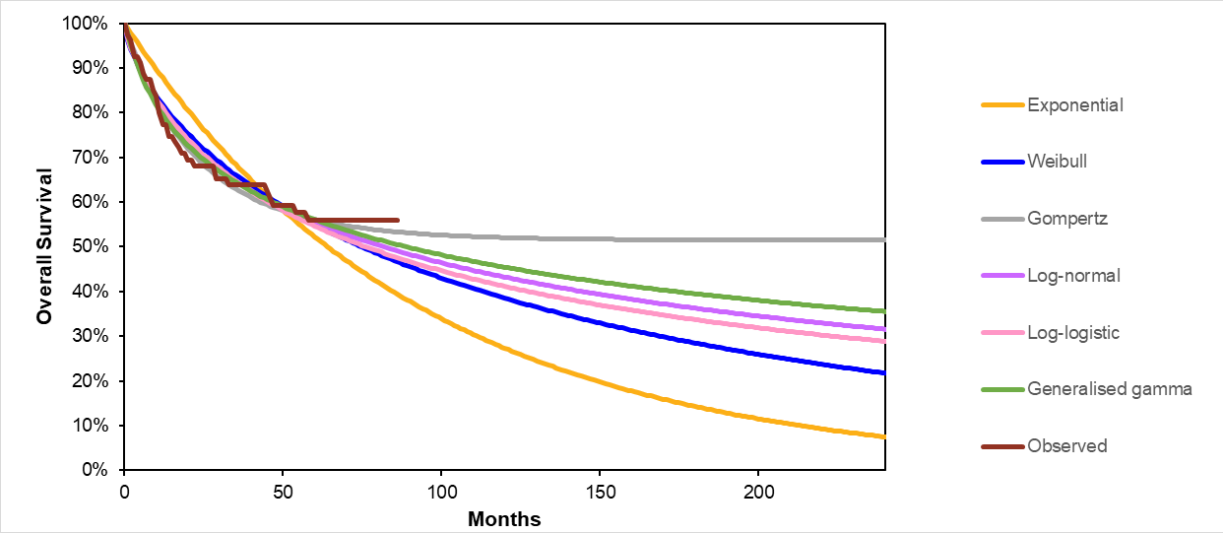
Table 35, and the extrapolations of OS using each model up to 20 years is presented in Figure 27 for all functions.

Table 35: Summary of goodness-of-fit data for tisagenlecleucel overall survival – standard parametric models

Distribution	AIC	BIC
Exponential	366.74	369.12
Weibull	361.73	366.50
Gompertz	**358.67**	**363.44**
Lognormal	358.95	363.71
Log-logistic	360.25	365.01
Generalised gamma	360.64	367.78

A smaller AIC or BIC value represents a better goodness of fit. Results in bold refer to distribution with the lowest AIC and BIC values.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 27: Extrapolation of tisagenlecleucel overall survival – standard parametric models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on the survival extrapolations shown.
Abbreviations: KM: Kaplan–Meier.

As demonstrated by Figure 27, with the possible exception of the Gompertz model, none of the standard parametric models were considered to adequately capture the change in the hazard function associated with the observed plateau in the tisagenlecleucel observed data, or the expected continuation of this plateau in the longer-term.

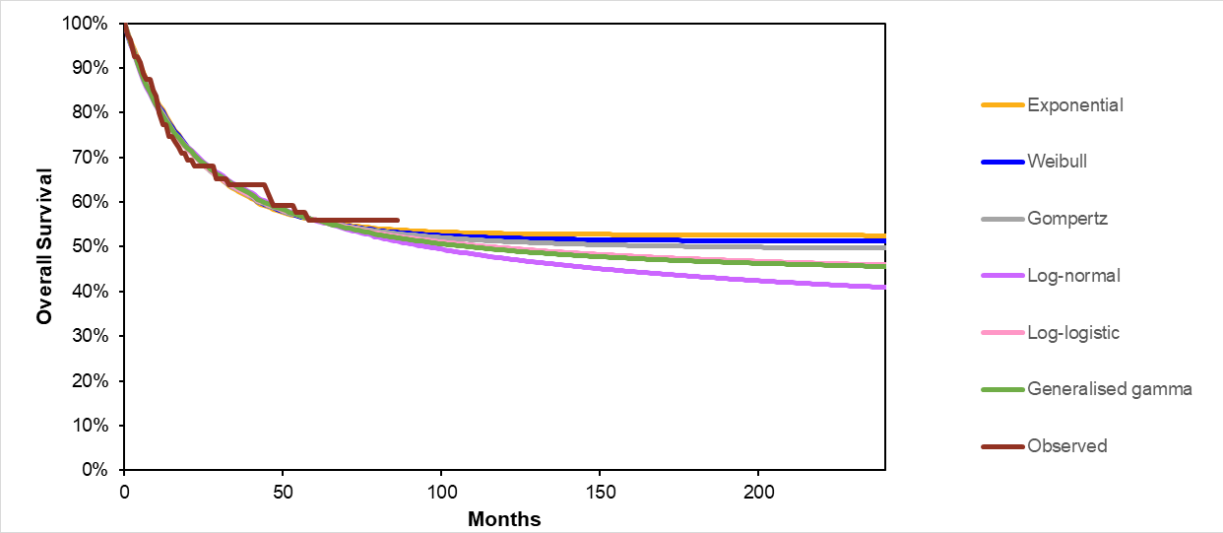
The AIC and BIC values together with the cure fraction rates for the various parametric mixture-cure models explored for the extrapolation of the OS data for tisagenlecleucel are summarised in Table 36. The extrapolations of OS using each model up to 20 years is presented in Figure 28.

Table 36: Summary of goodness-of-fit data for tisagenlecleucel overall survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	**359.00**	**363.77**	**52.9**
Weibull	360.82	367.96	51.6
Gompertz	360.53	367.68	41.7
Log-normal	360.46	367.61	32.8
Log-logistic	***360.33***	***367.48***	***42.4***
Generalised gamma	362.37	371.90	44.4

A smaller AIC or BIC value represents a better goodness of fit. Bold indicates model used as base case extrapolation. Results in bold refer to distribution with the lowest AIC and BIC values. Distribution in bold italics refer to the chosen distribution for the base case analysis.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 28: Extrapolation of tisagenlecleucel overall survival – mixture cure models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on survival extrapolations.
Abbreviations: KM: Kaplan–Meier.

In contrast to the standard parametric models, long-term survival profiles for mixture cure models were much more consistent, with all mixture cure models seen to reflect the plateau in the observed OS data and the expected continuation of this plateau in the longer-term. As previously described at the start of Section B.3.3.3, there are a number of reasons to consider it appropriate to reflect the existence of a subpopulation of 'cured' patients, as can be achieved through the mixture cure model approach. Given this, and the fact that the standard parametric survival models were seen to be unable to capture the observed plateau for tisagenlecleucel, the mixture cure models were considered most appropriate to model OS with tisagenlecleucel in the long-term, and a mixture cure model was ultimately selected to model OS with tisagenlecleucel within the base case economic analysis. The suitability of the extrapolations resulting from both standard parametric and mixture cure models were further validated with UK clinicians experienced in the

use of tisagenlecleucel in r/r B-cell ALL, who agreed that long-term survival predicted by mixture cure models was more plausible.[4]

The best-fitting mixture cure model by AIC and BIC for tisagenlecleucel OS was the exponential model and second best-fitting was the log-logistic, although differences in AIC were not material (<3 points difference from best- to worst-fitting). Visual fit to the Kaplan-Meier plot was also seen to be similar between the different mixture cure models. In order to ascertain the clinical plausibility of the survival extrapolations informed by the most recent ELIANA data cut, these were further validated with clinicians. All clinicians' estimates of long-term survival aligned with that predicted by the log-logistic and generalised gamma models (see Table 37 below), and clinicians agreed that these were most reflective of UK clinical practice for r/r B-cell ALL. These two curves were considered most appropriate to inform OS for tisagenlecleucel in the model. As the more conservative estimate, the log-logistic model was chosen over the generalised gamma in the base case analysis. The chosen log-logistic extrapolation also predicted 42.4% of patients in the tisagenlecleucel arm of the model to be cured (the "cure fraction"), which was well aligned to the average cure fraction estimated by clinicians (most likely value: 40% [lowest to highest plausible estimate: 25–57%]), and predicted survival for the log-logistic model at all timepoints was very similar to the most likely values estimated by the clinicians.

Table 37: Clinician and model estimates of OS for tisagenlecleucel

Category	Curve	OS (% surviving) at each timepoint					Cure fraction (%)
		1 yr	2 yrs	5 yrs	10 yrs	20 yrs	
KM	-	77.4	68.1	56.0	-	-	-
Average clinician estimates	Lowest plausible estimate	58	48	40	30	27	25.0
	Most likely estimate	**76**	**68**	**54**	**47**	**42**	**40.0**
	Highest plausible estimate	85	75	63	57	55	56.7
Standard parametric models	Exponential	88	77	52	27	7	-
	Weibull	82	73	55	38	22	-
	Gompertz	80	69	56	52	51	
	Log-normal	80	71	56	43	32	-
	Log-logistic	81	71	55	41	29	-
	Generalised gamma	80	70	56	45	35	-
Mixture cure models	Exponential	81	69	56	53	53	52.9
	Weibull	80	69	56	52	51	51.6
	Gompertz	80	69	56	51	50	41.7
	Log-normal	79	70	56	47	41	32.8
	Log-logistic	**79**	**69**	**56**	**50**	**46**	**42.4**
	Generalised gamma	79	69	56	49	46	44.4

Bold text indicates base case analysis and most likely estimate of average clinician estimates
Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Blinatumomab

For blinatumomab, pseudo-IPD for OS were generated using the algorithm described by Guyot *et al.* (2012) from the study by von Stackelberg *et al.* (2016),[7, 133] which was considered appropriate for decision making in the original submission (TA554), and has been further validated by UK clinicians, who considered it to be the most appropriate source given its length of follow-up and the inclusion of paediatric patients.[4, 9]

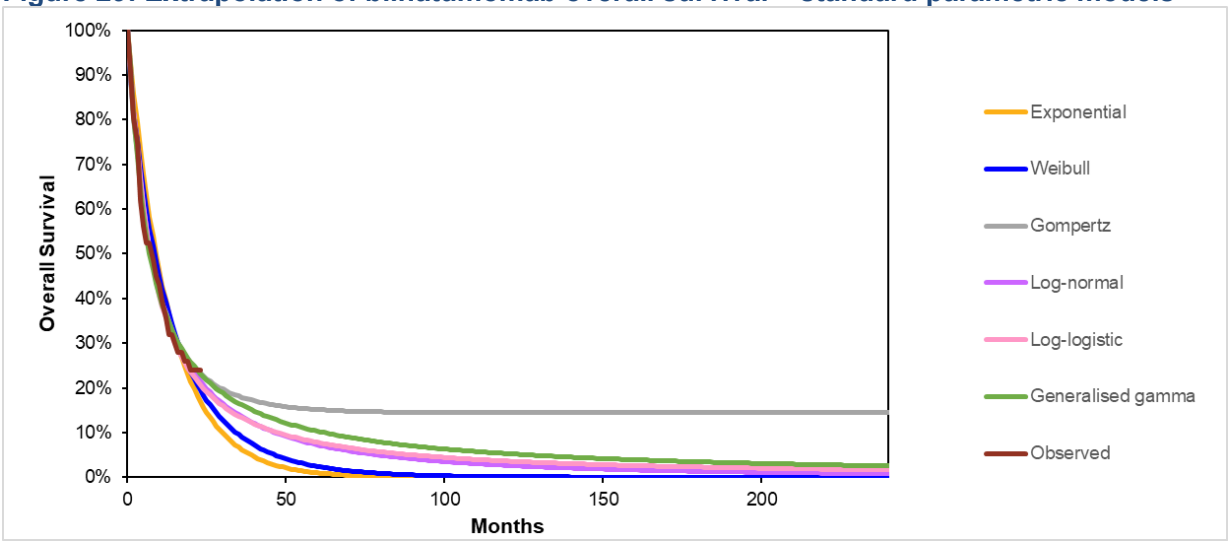
The AIC and BIC values for the various parametric models that were explored for the extrapolation of the OS data for blinatumomab are summarised in Table 38, and the extrapolations of OS using each model up to 20 years are presented in Figure 29 for all functions.

Table 38: Summary of goodness-of-fit data for blinatumomab overall survival – standard parametric models

Distribution	AIC	BIC
Exponential	343.79	346.04
Weibull	344.05	348.55
Gompertz	340.07	344.56
Lognormal	**337.83**	**342.32**
Log-logistic	339.31	343.81
Generalised gamma	339.12	345.87

A smaller AIC or BIC value represents a better goodness of fit. Results in bold refer to distribution with the lowest AIC and BIC values.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 29: Extrapolation of blinatumomab overall survival – standard parametric models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on the survival extrapolations shown.
Abbreviations: KM: Kaplan–Meier.

For blinatumomab, the best-fitting curves by AIC and BIC were the log-normal, exponential, and log-logistic. All three models provided a similar statistical and visual fit, with the lognormal function associated with the lowest AIC and BIC (see Table 39) and a reasonable visual fit to the Kaplan-Meier data (see Figure 29).[7] In the long-term, however, the choice of parametric distribution was

seen to significantly influence the survival projection, with the Gompertz presenting the most optimistic extrapolation of and the exponential the most pessimistic.

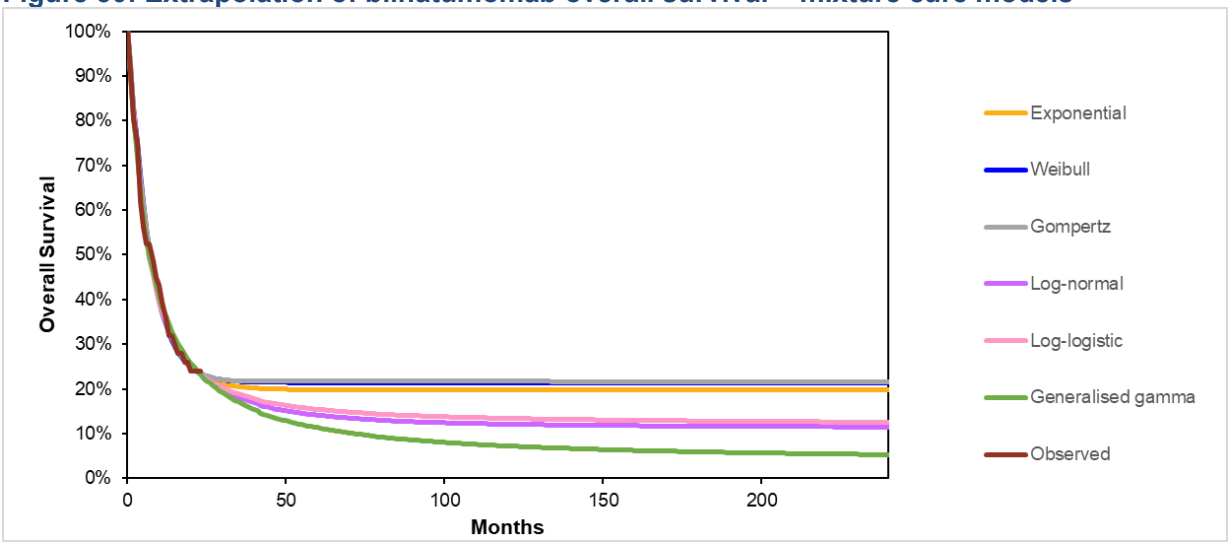
Clinical expert feedback gathered as part of the original appraisal (TA554) was that blinatumomab does not represent a curative therapy.[14] Clinical expert feedback sought as part of this submission indicated that blinatumomab is a bridging therapy to SCT.[4] Given allo-SCT is curative, for patients who are able to be treated successfully with an allo-SCT following blinatumomab-induced remission, there is the potential to achieve a cure. In the von Stackelberg *et al.* (2016) study used to inform blinatumomab effectiveness estimates in the model, 34.3% of patients went on to receive subsequent allo-SCT: a proportion of these would be expected to achieve successful outcomes with transplant and be cured of pALL. Therefore, mixture cure models were also explored to extrapolate the blinatumomab OS data. The AIC and BIC values together with the cure fraction rates for the various parametric functions explored for the mixture cure models are summarised in Table 39. The extrapolations of OS using each model up to 20 years are presented in Figure 30.

Table 39: Summary of goodness-of-fit data for blinatumomab overall survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	**339.62**	**344.12**	**19.8%**
Weibull	341.08	347.82	21.4%
Gompertz	341.52	348.26	21.7%
Lognormal	***339.19***	***345.94***	***11.4%***
Log-logistic	340.23	346.98	12.1%
Generalised gamma	341.12	350.11	3.9%

A smaller AIC or BIC value represents a better goodness of fit. Results in bold refer to distribution with the lowest AIC and BIC values. Distribution in bold italics refer to the chosen distribution for the base case analysis.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 30: Extrapolation of blinatumomab overall survival – mixture cure models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on the survival extrapolations shown.
Abbreviations: KM: Kaplan–Meier.

The mixture cure models were associated with similar AIC values; BIC values varied a little more but were still within approximately 6 points of each other in the majority of cases. The main difference between the mixture cure models was in the estimated cure fraction and hence the survival projection in the long term, with the cure fraction estimate varying between 3.9% (generalised gamma, most pessimistic) and 21.7% (Gompertz, most optimistic). Given the use of subsequent allo-SCT in a proportion of patients provides the potential for a cure, for consistency with the base case approach to modelling tisagenlecleucel, mixture cure models were considered more appropriate for modelling survival for blinatumomab in this submission, in line with the approach taken in the original submission (TA554).[9] Standard parametric extrapolations for blinatumomab were generally deemed too pessimistic, and were not considered further for inclusion in the model.

In the original submission (TA554), the logistic and lognormal mixture cure models were considered for extrapolation of blinatumomab OS data, and were thus considered as the most relevant candidate models for this submission.[9] The lognormal mixture cure model was selected for the base case, on the basis that this model had slightly better statistical fit by AIC and BIC than the log-logistic mixture cure model.

The cure fraction predicted by the lognormal model was 11.4%. This value is consistent with the proportion of patients expected to be cured following allo-SCT in the von Stackelberg *et al.* (2016) study;[7] clinical experts estimated the proportion of patients who achieve cure following allo-SCT to be approximately 40%, corresponding to a cure fraction of approximately 14% based on the allo-SCT rate reported in von Stackelberg *et al.* (2016) (34.3%).[4, 7]

Salvage chemotherapy (FLAG-IDA)

In the absence of any published OS data for salvage chemotherapy (FLAG-IDA), pseudo-IPD for OS were generated using the algorithm described by Guyot *et al.* (2012) from the clofarabine monotherapy study published by Jeha *et al.* (2006).[8, 133]

In the original submission for tisagenlecleucel in this indication (TA554) the use of these data were validated by UK clinical experts experienced in the treatment of r/r B-cell ALL in the paediatric and young adult setting, and stated that survival outcomes with the FLAG-IDA regimen could be considered comparable to those observed with clofarabine monotherapy.[14]

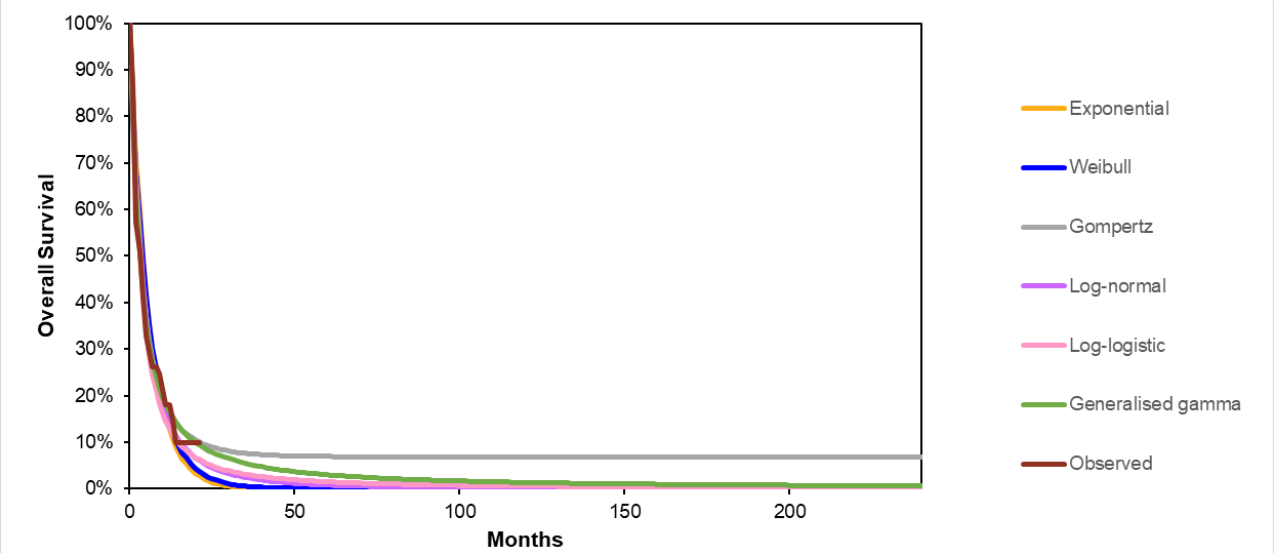
The AIC and BIC values for the various parametric models that were explored for the extrapolation of the OS data for salvage chemotherapy (FLAG-IDA) are summarised in Table 40 and the extrapolations of OS using each model up to 20 years are presented in Figure 31 for all functions.

Table 40: Summary of goodness-of-fit data for salvage chemotherapy (FLAG-IDA) overall survival – standard parametric models

Distribution	AIC	BIC
Exponential	261.42	263.53
Weibull	262.77	266.99
Gompertz	257.34	261.56
Lognormal	**252.07**	**256.29**
Log-logistic	252.87	257.09
Generalised gamma	251.93	258.26

A smaller AIC or BIC value represents a better goodness of fit. Results in bold refer to distribution with the lowest AIC and BIC values.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor.

Figure 31: Extrapolation of salvage chemotherapy (FLAG-IDA) overall survival – standard parametric models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on the survival extrapolations shown.
Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin;; G-CSF: granulocyte-colony stimulating factor; KM: Kaplan–Meier.

For salvage chemotherapy (FLAG-IDA), the generalised gamma distribution provided the best statistical fit to the Jeha *et al.* (2006) OS data in terms of AIC.[8] The log-logistic, lognormal, generalised gamma were the three best-fitting distributions across AIC and BIC generally. The lognormal and log-logistic functions were seen to produce an inferior fit on visual inspection against the Kaplan-Meier curve.

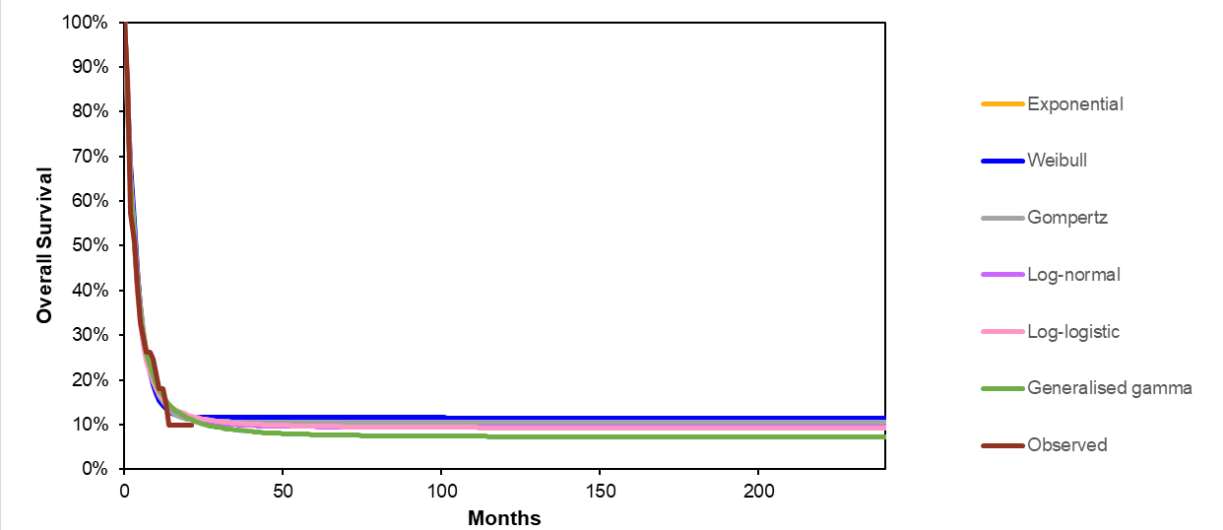
As for other comparators, clinical expert feedback sought as part of this submission indicated that salvage chemotherapy does not represent a curative therapy, but that for patients treated successfully with a subsequent allo-SCT there is the potential to achieve a cure.[4] Mixture cure models were also explored for the salvage chemotherapy OS profile. The AIC and BIC values together with the cure fraction rates for the various parametric functions explored for the mixture cure models are summarised in Table 41. The extrapolations of OS using each model up to 20 years is presented in Figure 32.

Table 41: Summary of goodness-of-fit data for salvage chemotherapy (FLAG-IDA) overall survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	256.68	260.90	10.6%
Weibull	257.50	263.83	11.5%
Gompertz	258.68	265.01	10.6%
Lognormal	***251.83***	***258.16***	***9.4%***
Log-logistic	252.69	259.02	9.2%
Generalised gamma	253.59	262.03	7.2%

A smaller AIC or BIC value represents a better goodness of fit. Results in bold italics refer to distribution with the lowest AIC and BIC values and the chosen distribution for the base case analysis.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor.

Figure 32: Extrapolation of salvage chemotherapy (FLAG-IDA) overall survival – mixture cure models



Extrapolation curves are fitted based on KM data with no subsequent adjustments (i.e. before the capping of general population mortality), Given the starting age of the population, such general population mortality adjustments would have little impact on the survival extrapolations shown.
Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; KM: Kaplan–Meier.

The best-fitting mixture cure models by AIC and BIC were the lognormal, log-logistic and generalised gamma, and these three were also seen to be the best fitting by visual inspection alongside the Kaplan-Meier data. All mixture cure models estimated a similar cure fraction of between 7.2% and 11.5%.

In order to select the base case curve to model OS with salvage chemotherapy (FLAG-IDA), the clinical plausibility of the survival estimates for the best fitting models amongst the standard parametric, and mixture cure model approaches was considered.

When previously presented to UK clinical experts as part of the original appraisal, the feedback was that the mixture cure models projected survival estimates that were too optimistic in the long-term compared to their experience of the survival outcomes observed in UK clinical practice for patients treated with salvage chemotherapy, even when accounting for a proportion of these patients going on to receive allo-SCT as per the Jeha *et al.* (2006) study (14.75%).[8, 14] Clinical expert feedback received in the original appraisal was clear that the majority of patients in relapse

post-transplant or in second or later relapse treated with salvage chemotherapy would not go on to receive an allo-SCT, and that survival outcomes for these patients are extremely poor, with very few patients expected to survive more than 2 years.[14] This is in stark contrast to the feedback from clinical experts received as part of this submission, which suggests that patients would not be treated with FLAG-IDA on a palliative basis, and that only a small percentage of patients would receive FLAG-IDA without possibility of subsequent transplant, as discussed above.[4] As discussed in Section B.3.2.3, clinical expectations around predicted survival for patients treated with salvage chemotherapy should be interpreted with caution given use of salvage chemotherapy in current clinical practice may not reflect the full population of relevance for this appraisal, which includes patients that are not suitable for subsequent allo-SCT.

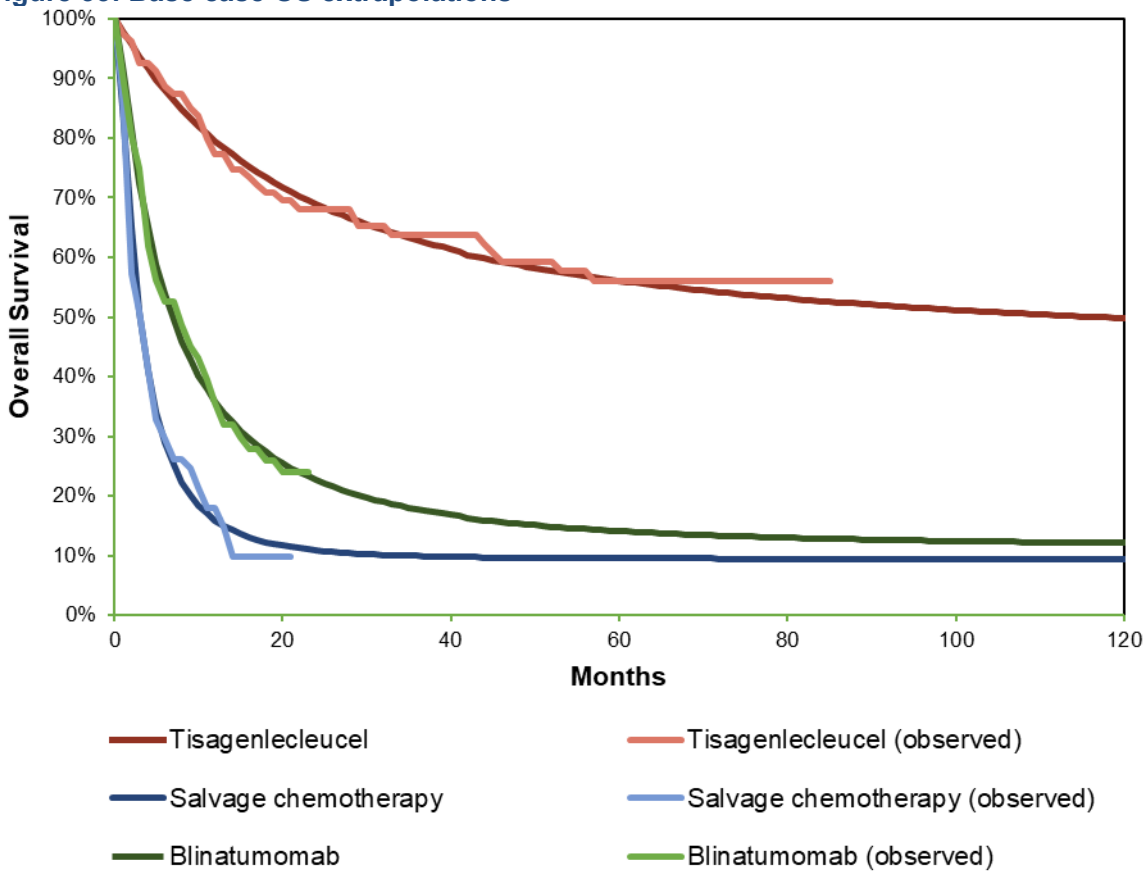
The mixture cure models predicted a long-term cured population of between 7.2–11.5%. These cure fractions are broadly consistent with average cure fraction predicted by the clinicians consulted as part of this appraisal (clinicians' averaged estimates: most likely value of 13.8%[lowest plausible to highest plausible: 3.0–24.3%]).[4] Considering that 14.75% of patients treated with salvage chemotherapy went on to allo-SCT in the Jeha *et al.* (2006) study, cure fractions of ~7–12% would imply that ~50% of patients treated with allo-SCT following salvage chemotherapy achieve successful treatment, post-transplant survival and hence cure.[4, 8] Mixture cure models were considered overly optimistic by clinical experts consulted in the original appraisal, and a standard parametric generalised-gamma distribution was originally used to extrapolate OS in the base case.[14] This is corroborated by feedback from clinical experts received as part of this appraisal estimating the proportion of patients who achieve cure following allo-SCT to be approximately 40%.[4]

The NICE committee in TA554 noted that long-term OS was likely underestimated in the base case, however overestimated by the ERG's preferred model (a mixture-cure model based on Kuhlen *et al.* [2017]).[9] Clinical experts consulted as part of this appraisal agreed that survival should be lower than predicted by the ERG-preferred models, but that cure was plausible for a proportion of patients.[4] Therefore, in this submission, the lognormal mixture cure model was selected for the base case, since it was associated with the best statistical fit, and the cure fraction represents a conservative estimate of the cured population based on the rate of allo-SCT reported in the Jeha *et al.* (2006), which informs the base case allo-SCT rates for salvage chemotherapy in the model.[8]

Summary of base case extrapolations (OS)

Figure 33 presents the base case OS extrapolations for tisagenlecleucel (mixture cure – log-logistic), salvage chemotherapy (mixture cure – lognormal) and blinatumomab (mixture cure – lognormal).

Figure 33: Base case OS extrapolations



Abbreviations: OS: overall survival.

The base case models for OS for tisagenlecleucel, blinatumomab and salvage chemotherapy (FLAG-IDA) were mixture cure models, aligned to the ERG preference in the original appraisal (TA554).[9]

The OS profile was bounded by general population mortality, adjusted by a SMR, with the same mortality risk applied to all treatments, to ensure that the mortality rate could not exceed expected survival for long-term ALL survivors. A literature review conducted to identify publications to inform long-term survival for the study target population (registry or SMR studies) identified four SMR publications for paediatric and young adult ALL long-term survivors as being of the most relevant evidence.[119, 134-136] However, an SMR of 4 was considered appropriate by UK clinical expert feedback (the SMR was estimated to be 3.7 [lowest to highest plausible estimates: 2.2–7.3]) and was therefore used in the base case in favour of literature values.[4] In the NICE appraisal of brexucabtagene autoleucel in r/r B-cell ALL (TA893), the committee considered an SMR of 3 appropriate, indicating a SMR of 4 to be conservative.[58] The SMR input derived from MacArthur *et al.* (2007) was also evaluated in scenario analyses (see Section B.3.10.3).[119] These SMR input sources are summarised in Table 42.

Table 42: Long-term survival input sources

Publication	Population	Sample Size	SMR Measure
Base case			
Clinical opinion[4]	Paediatric and young adult patients aged up to 25 with r/r B-cell ALL	N/A	SMR for long-term ALL survivors: **4**
Scenario analyses			
MacArthur *et al.* 2007[119]	Individuals less than 20 years of age diagnosed with cancer who survived 5 years or more after diagnosis.	Overall sample size: 2,354; Sample size for ALL patients: 429	SMR for childhood cancer 5-year survivors: **9.05**

[58]**Abbreviations:** ALL, acute lymphoblastic leukaemia; N/A; not applicable; r/r: relapsed or refractory; SMR, standardised mortality ratio.
Source: Novartis Data on File;[4] MacArthur *et al.* (2007);[119] TA893.[58]

Event-free survival

Tisagenlecleucel

For tisagenlecleucel, the EFS IPD was used directly from the ELIANA trial (data cut-off 17th Nov 2022) to model EFS.[2] Consistent with the approach used to extrapolate OS, standard parametric models and mixture cure models were considered for extrapolation of the EFS data beyond the observed trial period. The uncertainties surrounding the extrapolation of EFS identified by the ERG in the original appraisal (TA554) due to the short follow-up period and small patient numbers have since been mitigated in the current submission given the availability of data with long-term follow-up.[2, 9]

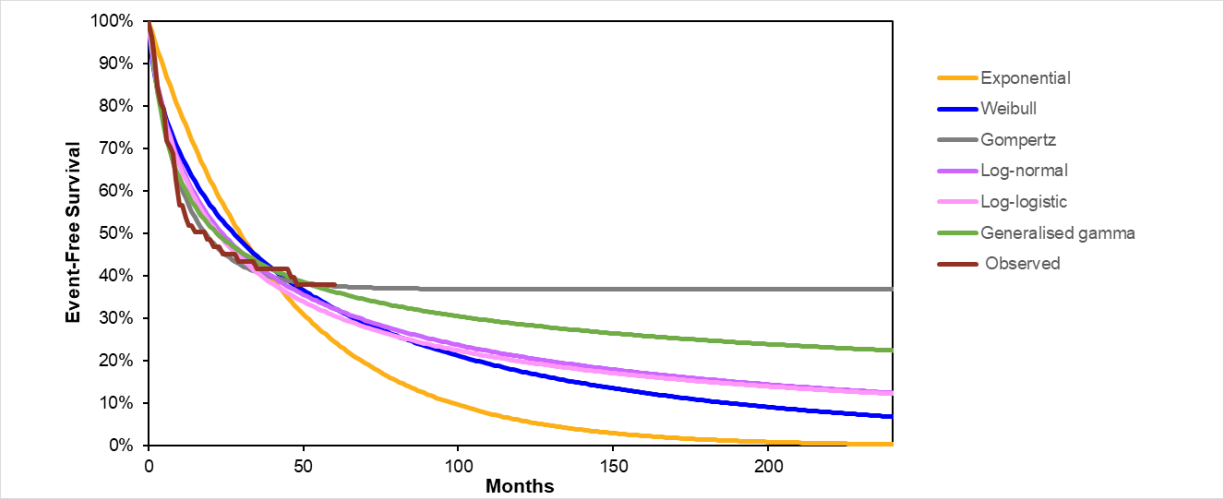
The AIC and BIC values for the various parametric models that were explored for the extrapolation of the EFS data for tisagenlecleucel are summarised in Table 43, and the extrapolations of EFS using these models are presented in Figure 34 (for all functions up to 10 years).

Table 43: Summary of goodness-of-fit data for tisagenlecleucel event-free survival – standard parametric models

Distribution	AIC	BIC
Exponential	401.45	403.83
Weibull	386.83	391.60
Gompertz	**371.99**	**376.75**
Lognormal	377.38	382.14
Log-logistic	380.24	385.01
Generalised gamma	374.03	381.18

A smaller AIC or BIC value represents a better goodness of fit. Results in bold refer to distribution with the lowest AIC and BIC values.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 34: Extrapolation of tisagenlecleucel event-free survival – standard parametric



None of the standard parametric models were seen to fit the Kaplan-Meier data very well visually, or capture the observed plateau and the expected continuation of this plateau in the longer-term. Furthermore, as a mixture cure model had been used for the modelling of OS, it was considered appropriate to also use a mixture cure model for extrapolation of EFS. EFS extrapolation curves were presented to UK clinical experts consulted as part of this appraisal who confirmed that the EFS and OS curves should be closely matched and were representative of UK clinical practice.[4]

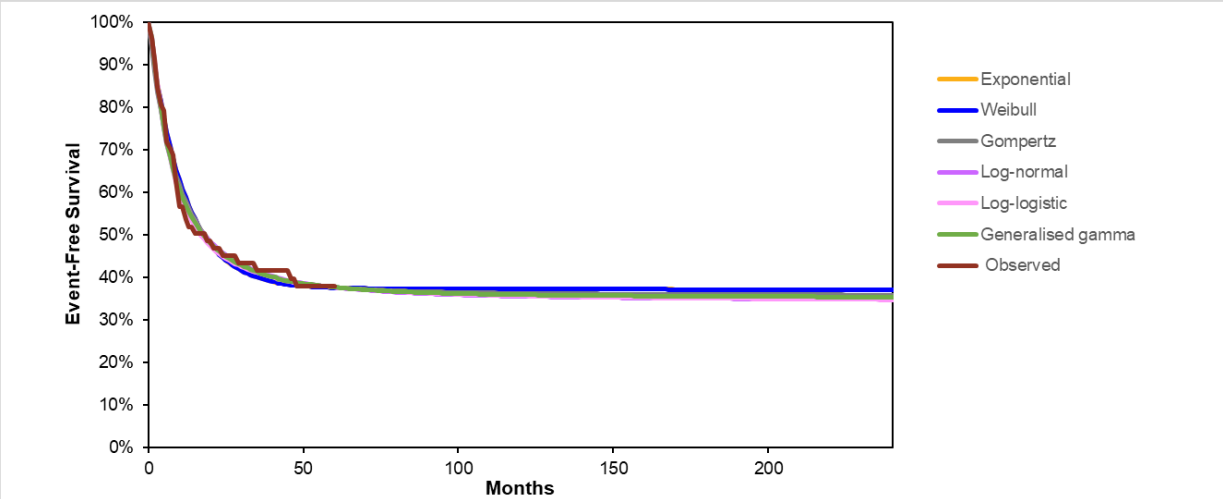
The AIC and BIC values of the mixture cure models are summarised in Table 44. The extrapolations of EFS up to 10 years using these mixture cure models are provided in Figure 35.

Table 44: Summary of goodness-of-fit data for tisagenlecleucel event-free survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	372.57	377.34	37.4%
Weibull	374.57	381.72	37.4%
Gompertz	373.71	380.85	35.0%
Lognormal	***371.58***	***378.72***	***34.9%***
Log-logistic	371.57	378.72	34.6%
Generalised gamma	373.54	383.07	35.6%

A smaller AIC or BIC value represents a better goodness of fit. Results in bold italics refer to distribution with the lowest AIC and BIC values and the chosen distribution for the base case analysis.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 35: Extrapolation of tisagenlecleucel event-free survival – mixture cure models



All the mixture cure models were associated with similar AIC values; BIC values varied a little more but were still within approximately 6 points of each in the majority of cases. Whilst some variation in cure fractions was observed in the original submission, given the maturity of the longer-term EFS data, the estimated cure fractions were largely similar across models (ranging from 34.6% to 37.4%). The log-logistic model was selected as the base case model for tisagenlecleucel EFS based on its conservative estimate of 34.6% cure rate, and aligned well with clinicians' survival estimates (see Table 45 below).[4]

Table 45: Clinician and model estimates of EFS for tisagenlecleucel

Category	Curve	EFS (% surviving) at each timepoint					Cure fraction (%)
		1 yr	2 yrs	5 yrs	10 yrs	20 yrs	
KM	-	53.6	45.1	38.0	-	-	-
Average clinician estimates	Lowest plausible estimate	37	28	18	15	13	25.0
	Most likely estimate	**57**	**45**	**35**	**33**	**28**	**40.0**
	Highest plausible estimate	68	57	48	43	42	56.7
Standard parametric models	Exponential	76	57	25	6	0	-
	Weibull	66	53	32	18	7	-
	Gompertz	58	46	38	37	37	-
	Log-normal	63	50	32	21	12	-
	Log-logistic	63	49	31	20	12	-
	Generalised gamma	60	49	36	29	22	-
Mixture cure models	Exponential	59	45	38	37	37	37.4
	Weibull	59	45	38	37	37	37.4
	Gompertz	58	46	38	36	36	35.0
	Log-normal	57	46	38	36	35	34.9
	Log-logistic	**56**	**45**	**38**	**36**	**35**	**34.6**
	Generalised gamma	57	46	38	36	35	35.6

Bold text indicates base case analysis and most likely estimate of average clinician estimates
Abbreviations: EFS: event-free survival; KM: Kaplan-Meier.

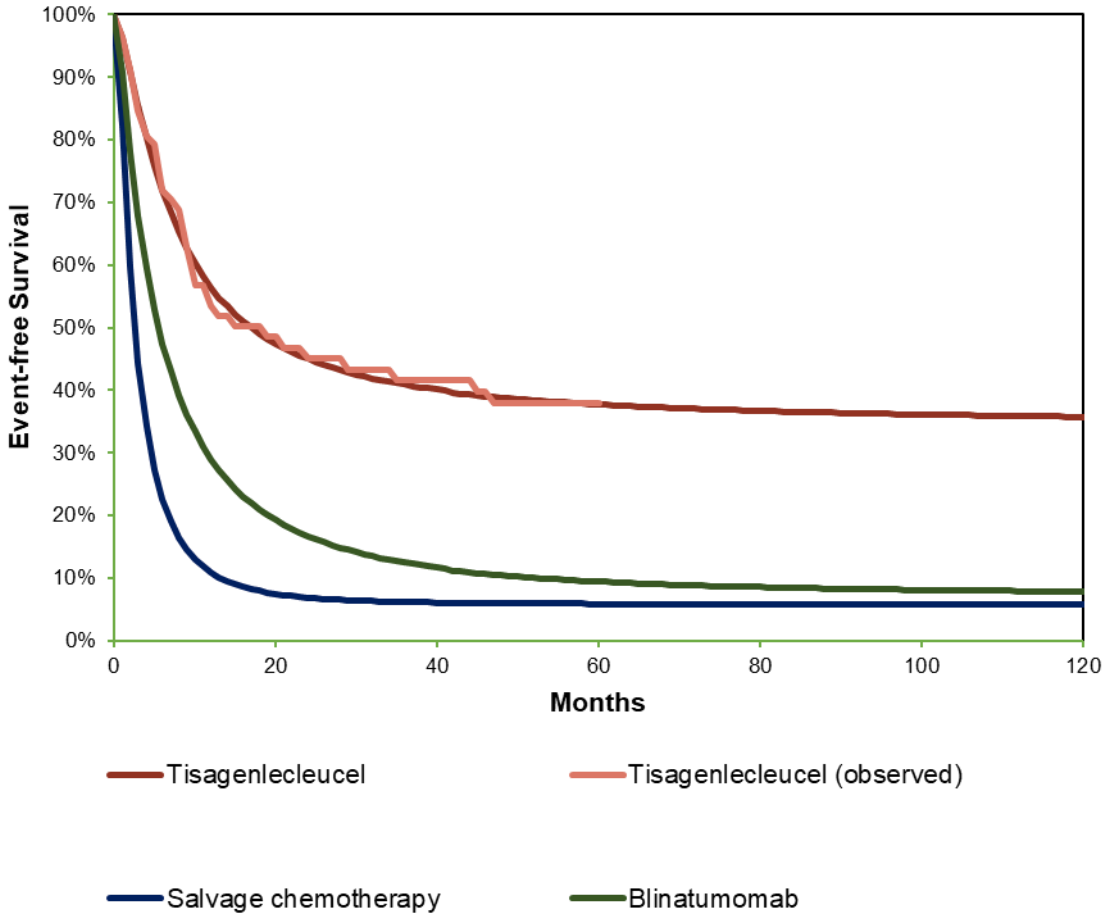
Comparators

EFS data were not available for blinatumomab and salvage chemotherapy (FLAG-IDA) from the von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) studies.[7, 8] As such, the EFS curves were derived from the available OS curves, consistent with the approach taken in the NICE mock appraisal, an approach which was accepted in the original appraisal (TA554).[9, 137] It was assumed that the cumulative hazard function for EFS would be proportional to the cumulative hazard function for OS. The ratio between EFS and OS was modelled based on data from the UK ALL study, a study of mitoxantrone in children with a first relapse of ALL.[54] Whilst it is acknowledged that the patient population of this study is not entirely in line with the patient population of interest of this appraisal, the UK ALL study was one of the only studies that reported both OS and EFS identified in the clinical SLR performed as part of the original submission (TA554). The latest SLR update performed identified one relevant study being in similar patient populations to the tisagenlecleucel clinical trials that reported both OS and EFS data whereby the study investigated clofarabine; however, OS was not defined in the study and the study reported a EFS/OS ratio of 1.[95] It was therefore considered that the UK ALL study provided the best available evidence to inform the derivation of the EFS curve. This assumption is considered to be justifiable on the basis that EFS is highly correlated with OS.[138] The proportional relationship between EFS and OS was assumed to continue up to Year 5, and EFS was assumed to be less than or equal to OS at all time points.

Base case extrapolations (EFS)

Figure 36 presents the base case EFS extrapolations for tisagenlecleucel (mixture cure – log-logistic), blinatumomab (cumulative HR based on mixture cure – log-normal for OS) and salvage chemotherapy (cumulative HR based on mixture cure – log-normal for OS).

Figure 36: Base case EFS extrapolations



Abbreviations: EFS: event-free survival.

B.3.3.4 Adverse events

Where data were available, any grade 3 or 4 AEs regardless of study-drug relationship that occurred in ≥5% of patients were included in the economic model. Consistent with the patient baseline characteristics and clinical efficacy inputs of the base case analysis, AE rates for tisagenlecleucel were derived from the patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=79) in ELIANA (DCO 17th Nov 2022).[2] For blinatumomab, AE rates were derived from von Stackelberg *et al.* (2016) and for salvage chemotherapy (FLAG-IDA), in the absence of any clinical evidence for FLAG-IDA, the AE rates from Jeha *et al.* (2006) were used.[7, 8] All sources of AE rates were therefore consistent with the clinical efficacy input sources used in the base case analysis as described in Section B.3.3.3. All AEs included within the model were reviewed by four UK clinical experts as part of the original submission (TA554), who agreed that no AEs with either a substantial cost or substantial effect on patient quality of life had been omitted from the analysis.[14]

Table 46: Incidence of Grade 3 or 4 adverse events included in the model

AEs	Tisagenlecleucel	Salvage chemotherapy (FLAG-IDA)	Blinatumomab
Source for AE rates	**ELIANA CSR (17th Nov 2022)[2,a]**	**Jeha *et al.* (2006)[8,b]**	**von Stackelberg *et al.* (2016)[7,c]**
Acute kidney injury	10.13%	-	-
Alanine aminotransferase increased	8.86%	-	15.71%
Anaemia	11.39%	-	35.71%
Anorexia	-	19.67%	-
Aspartate aminotransferase increased	13.92%	-	11.43%
Bacteraemia	2.53%	13.11%	-
Blood bilirubin increased	11.39%	-	-
Cytokine-release syndrome	48.10%	-	5.71%
Decreased appetite	15.19%	-	-
Dermatitis	-	11.48%	-
Diarrhoea	2.53%	13.11%	-
Encephalopathy	5.06%	-	-
Epistaxis	1.27%	13.11%	-
Febrile neutropenia	34.18%	49.18%	17.14%
Hallucination	-	13.11%	-
Hepatomegaly	1.27%	11.48%	-
Hyperglycaemia	6.33%	-	-
Hypertension	6.33%	9.84%	5.71%
Hypocalcaemia	6.33%	-	-
Hypogammaglobulinaemia	7.59%	-	-
Hypokalaemia	13.92%	-	17.14%
Hypophosphataemia	11.39%	-	-
Hypotension	20.25%	18.03%	-
Hypoxia	20.25%	-	-
Infection	49.37%	9.84%	-
Leukopenia	2.53%	-	10.00%
Lymphocyte count decreased	18.99%	-	-
Nausea	2.53%	16.39%	-
Neutropenia	11.39%	14.75%	17.14%
Neutrophil count decreased	26.58%	-	12.86%
Petechiae	-	11.48%	-
Platelet count decreased	18.99%	-	14.29%
Pleural effusion	3.80%	9.84%	-
Pneumonia	5.06%	9.84%	-
Pulmonary oedema	8.86%	-	-

Pyrexia	13.92%	14.75%	14.29%
Respiratory distress	1.27%	11.48%	-
Sepsis	3.80%	13.11%	-
Thrombocytopenia	11.39%	-	21.43%
White blood cell count decreased	21.52%	-	10.00%

Note: For transparency, AEs have been listed according to how the AE is reported in the relevant source. As such, some AEs may appear to be listed twice, but have been assumed to incur the same costs
[a]ELIANA CSR (17th Nov 2022). Based on grade 3 or 4 AEs, regardless of study drug relationship, occurring any time post tisagenlecleucel infusion in >5% patients.[2]
[b]Jeha *et al.* (2016). Based on grade ≥3 AEs, regardless of causality that occurred in ≥10% of patients in all cycles.[8]
[c]von Stackelberg *et al*. (2016). Based on AEs of worst grade ≥3 regardless of relationship to treatment that occurred in ≥5% of patients (who received the recommended dose of 5/15 μg/m^2/day in phase I or II) during the treatment period and until 30 days after the last treatment or before allogeneic hematopoietic stem-cell transplantation or start of chemotherapy.
Abbreviations: AE: adverse event; CRS: cytokine release syndrome; RBC: red blood cell; WBC: white blood cell.
Source: ELIANA CSR (17th Nov 2022);[2] Jeha *et al.* (2006);[8] von Stackelberg *et al.* (2016).[7]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

In the ELIANA trial, EQ-5D data were collected for patients aged 8 years and older. Two different versions of EQ-5D were used. EQ-5D-Y was used for patients aged between 8 and 12 years at study entry, and the general EQ-5D-3L was used for patients aged 13 years and above. As a validated value set for converting EQ-5D-Y to a utility score are not available for the UK population, the utility scores were derived based on the EQ-5D-3L data only.[139, 140] EQ-5D-3L scores were collected at baseline, Month 1 and Month 3, and then every 3 months until Month 24. Descriptive statistics on the EQ-5D-3L values were generated using patient-level EQ-5D-3L data from the latest ELIANA trial data cut (17th Nov 2022; n=36).[2, 9] A brief re-cap of the derivation of the EQ-5D-3L data can be found below whereby EQ-5D-3L values were calculated by the following categories corresponding to the following model health states:[2]

- **EQ-5D-3L measures for EFS:** any EQ-5D-3L assessments when patients are in the EFS state, i.e. on or after the treatment start date and before the date of relapse, treatment failure or death. EFS definition is consistent with the EFS definition used in the ELIANA trial protocol[80]
- **EQ-5D-3L measures for PD:** any EQ-5D-3L assessment when patients are in "Relapsed state before treatment" or "Post-EFS" categories. Relapsed state before treatment is defined as any assessments before tisagenlecleucel infusion, where patients were in relapsed/refractory state from prior treatments. Post-EFS after treatment is defined as any assessment on or after the EFS event or before the censoring date. For patients who experienced treatment failure, any assessments on or after the treatment failure date were considered as "Post-EFS"

EQ-5D-3L utility scores were calculated based on individual dimension scores and using UK preference-weights.[141] This analysis did not impute values for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit was excluded from the analysis for that visit. Results were estimated by using a generalised estimating equation (GEE) model with a robust variance estimator to account for correlation within patients' repeated assessments. Descriptive statistics of the EQ-5D utility values and the total sample size by the above health state categories are shown in Table 47.

Table 47: Descriptive statistics on EQ-5D utility values in ELIANA trial

Health States	N patients[a]	N assessments	Mean	SD
EFS	30	153	0.82	0.22
Before treatment/post-EFS	31	50	0.66	0.36

[a]The same patient can have multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state.
Abbreviations: EFS: event-free survival; EQ-5D: European quality of life 5 dimensions; SD: standard deviation.
Source: ELIANA CSR (17th Nov 2022).[2]

B.3.4.2 Mapping

Mapping was not used within this economic analysis.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted on 20th March 2023 as part of this submission to identify any relevant HRQoL studies reporting utility values in patients up to 25 years of age with r/r B-cell ALL. Details of the search strategy, study selection and results of this SLR are presented in Appendix H.

A total of 15 articles reporting on 13 unique HRQoL studies were included in the SLR, of which 14 were included from the electronic database searches and supplementary searches retrieved one additional article. Two publications reporting on two unique studies were prioritised for data extraction and are as follows: NoMA (2018) and Aristides *et al.* (2015).

Artistides *et al.* (2015) reported the mean EQ-5D utility score estimate for adult r/r B-cell ALL patients aged above 18 years old in the UK.[142] As the study did not include paediatric patients or present data separately for young adult patients (i.e. 18–25 years old), the study was not considered to be appropriate to inform the utility values for the r/r B-cell ALL population of interest considered in this submission.

NoMa (2018) was a single-technology appraisal of tisagenlecleucel for the treatment of paediatric and young adult r/r B-cell ALL patients aged up to 25 years old and reported the health state utilities of interest to this submission. However, given the very limited sample size available for EQ-5D data used in this submission (from the ELIANA trial), the utility values from NoMa were considered to be limited in its statistical power to inform the economic modelling of the r/r B-cell ALL population in this submission.

Given the limitations of both studies to inform the utility values in the economic model, studies which had been identified in the SLR conducted as part of the original submission (TA554) were used instead. A brief re-cap of the assessment of the identified studies (Kelly *et al.* [2015] and Sung *et al.* [2003]) are as follows, noting that these sources were largely accepted by the ERG with further elaboration of the ERG-preferred utility source listed below.

Kelly *et al.* (2015) used a decision analysis to evaluate cranial radiation therapy for paediatric T-cell ALL patients and performed a SLR of utility studies as part of the analysis.[106] While the study focused on T-cell ALL, the SLR of utilities included all forms of ALL. The Kelly *et al.* (2015) study used existing mapping functions to convert generic quality-of-life measure (i.e. SF-36 and CHRIs) to preference-based utility estimates (i.e. HUI2 and EQ-5D). The utility inputs for health states *in the state of relapse* and *cured after relapse* from the Kelly *et al.* (2015) were used as health state utility values by the York group in the NICE mock appraisal of regenerative therapies. As

mentioned above, given the limited sample size available for EQ-5D data from the ELIANA trial, the utility values from Kelly *et al.* (2015) were similarly considered appropriate to inform the utility values for the PD and EFS states, respectively, in the base case analysis for the economic model presented in this submission. However, for completeness, a scenario analysis (as suggested by the ERG in the original appraisal [TA554]) has been conducted where the ELIANA EQ-5D utilities were used to inform the economic model for the first 2 years, followed by Kelly *et al.* (2015) to inform long-term survival due to the previous lack of long-term follow-up data for ELIANA.

B.3.4.4 Adverse reactions

Sung *et al.* (2003) reported physician elicited utility estimates for acute myeloid leukaemia patients who survived post transplantation without recurrent disease.[143] Inputs for treatment disutility included within the economic analysis were based on estimates from the study by Sung *et al.* (2003).[143] For all patients, a utility decrement of -0.42 was applied, regardless of therapy received, i.e. tisagenlecleucel was assumed to have the same treatment disutility as salvage chemotherapy (FLAG-IDA) and blinatumomab. This decrement was assumed to apply for the average duration of hospitalisation stay per treatment, hence the duration of the disutility differed between treatments. This approach was validated by four UK clinical experts consulted as part of the original appraisal (TA554), who described that treatment with both tisagenlecleucel and salvage chemotherapy involved patients experiencing a number of AEs at the beginning of treatment, and then following recovery within hospital, patients would be unlikely to experience many AEs.[14] For blinatumomab, applying treatment-related disutility based on hospitalisation is less reflective of clinical experience given patients may be likely to experience AEs (albeit to a lesser degree) throughout the treatment period. However, this assumption had been previously explored in a scenario analysis in the original appraisal (TA554) for blinatumomab which found minimal impact on the ICER. Hence, the base-case assumption was retained in this submission and no scenario analyses were performed. The modelling of AEs in the original appraisal (TA554) was considered to be appropriate by the ERG and has been retained in this submission.[9]

For patients undergoing a subsequent allo-SCT, a utility decrement of -0.57 was applied for 1 year. As the study by Sung *et al.* (2003) did not report any estimate of duration associated with the reported disutility estimates, the disutility associated with the receipt of a subsequent allo-SCT was assumed to last for one year post treatment initiation, which was consistent with the NICE mock appraisal.[137] The ERG in TA554 noted that utility decrements estimated by Sung *et al. (*2003) may overestimate the duration of its persistence, and instead presented a scenario which applied the Sung *et al.* (2003) decrement for 3 months, followed by a smaller decrement of -0.13 for 9 months based on Felder-Puig *et al.* (2006). This approach has been recreated and explored as a scenario analysis presented in Section B.3.10.3. The rates of subsequent allo-SCT were obtained from the same clinical trial studies used for the efficacy estimation.[2, 7, 8] The above estimates are assumed to capture the utility decrements for all short-term AEs associated with treatment, with the exception of CRS.

Additional treatment disutilities were considered for patients experiencing grade 3 or 4 CRS. The CRS rate for tisagenlecleucel was derived from the ELIANA trial, and the rates for blinatumomab were derived from von Stackelberg *et al.* (2016).[2, 7] Patients experiencing grade 3 or 4 CRS were assumed to have a utility of 0 (a disutility of -0.91) for the average duration of ICU stay associated with CRS based on the ELIANA trial (17th Nov 2022).[2] In addition, for patients receiving tisagenlecleucel infusion, an additional treatment disutility was also considered for ICU stays not due to CRS by assuming that patients in the ICU would have a utility value of 0 (a disutility of -0.91).

A summary of the disutility values included within the economic analysis is provided in Section B.3.4.5.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Age-related disutility decrements

As the utility inputs for the model were estimated based on a paediatric and adolescent population, the model considered additional age-related decrements as the modelled population became older over the modelled time horizon. The decrements were derived from Health Survey for England (HSE) 2014, as recommended by the NICE DSU.[144] Adjustments were calculated for each age range to reflect the impact associated with age on utility. For each given age, the same adjustment was applied to all utility inputs regardless of health states.

Utility values used within the economic model

A summary of the utility values used within the economic model is provided in Table 48. Given the very limited sample size available for EQ-5D data from the ELIANA trial, the utility values from the study by Kelly *et al.* (2015)[106] were used in the base case economic analysis, in line with the approach taken by the company in TA554 and accepted by committee as suitable for decision-making. As noted in the original appraisal, there are some limitations with use of the utility values from Kelly *et al.* (2015); most notably that the HRQoL data were not collected directly from the population of the tisagenlecleucel studies and, in the case of the EFS utility value (0.91), the health state preference measure used was HUI2 rather than EQ-5D. However, these utility values were derived from large studies and corresponded to health states representative of the EFS and PD health states defined in this model. Furthermore, these utility values were used by the York group in the NICE mock appraisal of regenerative therapies.

As noted in the original appraisal, the ERG preferred the use of ELIANA EQ-5D to model utility values for the first two years followed by long-term survival value derived from Kelly *et al.* (2015). Despite the availability of long-term follow-up data from ELIANA at the time of this submission, the sample size of ELIANA EQ-5D data remains limited (utility values for both health states are based on only ~30 patients).

In light of the limited sample size of the ELIANA EQ-5D data and the lack of relevant sources for utility values identified by the SLR as mentioned in Section B.3.4.3, the values from Kelly *et al.* (2015) were considered most appropriate for the base case analysis, however utility values derived from the ELIANA trial were explored as a scenario analysis. Given the assumption that any patients in the model that were still alive at 5 years are deemed to be effectively cured, it was assumed that these patients would be associated with the utility value of the EFS health state, regardless of the health state they were currently in, or the treatment being received (long-term survival utility).

Table 48: Utility values used within the economic model

Parameter	Utility/disutility input	Duration (days)	% of patients	Source / Assumptions
Health state utility values (base case)				
EFS	0.91 (SE 0.02)	N/A	N/A	Kelly *et al.* (2015)[106]
PD	0.75 (SE 0.16)	N/A		
Long-term survival	0.91 (SE 0.02)	N/A		
Health state utility values (scenario analysis)				
EFS	0.82 (SE 0.03)	N/A	N/A	ELIANA (DCO 17th Nov 2022)[2]
PD	0.66 (SE 0.07)	N/A		
Treatment disutility				
Tisagenlecleucel	-0.42	25.85	N/A	Sung *et al.* (2003)[143]
Salvage chemotherapy (FLAG-IDA)	-0.42	21.00		
Blinatumomab	-0.42	9.24		
Grade 3 or 4 CRS (ICU stay)				
Tisagenlecleucel	-0.91	11.10	48.10%	ELIANA (DCO 17th Nov 2022)[2]
Blinatumomab	-0.91	11.10	5.71%	ELIANA (DCO 17th Nov 2022)[2], von Stackelberg *et al.* (2016) (% of patients)[7]
ICU stay not due to CRS				
Tisagenlecleucel	-0.91	1.74	N/A	ELIANA (DCO 17th Nov 2022)[2]
Subsequent allo-SCT disutility				
Tisagenlecleucel	-0.57	365	22.78%	ELIANA (DCO 17th Nov 2022)[2]
Salvage chemotherapy (FLAG-IDA)	-0.57	365	14.75%	Jeha *et al.* (2006)[8]
Blinatumomab	-0.57	365	34.29%	von Stackelberg *et al.* (2016)[7]
Age-related utilities[a,b]				
Age 1-22	1.00	N/A	N/A	HSE (2014)[144]
Age 23-29	0.99			
Age 30-34	0.98			
Age 35-39	0.97			
Age 40-43	0.96			
Age 44-47	0.95			
Age 48-50	0.94			
Age 51-53	0.93			
Age 54-56	0.92			
Age 57-59	0.91			
Age 60-62	0.90			
Age 63-64	0.89			
Age 65-67	0.88			

Age 68-69	0.87			
Age 70-71	0.86			
Age 72-73	0.85			
Age 74-75	0.84			

[a]In the absence of paediatric data, age-related utility values for ages 1-16 have been assumed to be equal to that of age 16.
[b]Adjustments were calculated for each age range to reflect the impact associated with age on utility. For each given age, the same adjustment was applied to all utility inputs regardless of health states. Age-related utilities for ages 16-101 can be found in greater detail in the economic model.
Abbreviations: CRS: cytokine-release syndrome; DCO: data cut-off; EFS: event-free survival; allo-SCT: haematopoietic stem cell transplantation; HSE: Health Survey for England; ICU: intensive care unit; N/A: not applicable; PD: progressive disease; VOD: veno-occlusive disease.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted on 20th March 2023 as part of this submission to identify cost and resource use data for patients aged up to 25 with r/r B-cell ALL. Full details of the search strategy are presented in Appendix I.

A total of 24 publications reporting on 22 unique studies were included in the SLR, of which 20 were included from the electronic database searches and 4 additional publications were retrieved from supplementary searches. Eight publications reporting on eight unique studies were prioritised for data extraction which included NoMA (2018), Boluda *et al.* (2019), Carey *et al.* (2022), Cool *et al.* (2021), Dombret *et al.* (2016), Lecat *et al.* (2019), Maertens *et al.* (2017) and a SMC appraisal of tisagenlecleucel (2019). Full details of these studies are presented in Appendix I.

The economic analysis was conducted from the NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Of the eight studies identified, only Lecat *et al.* (2019) and SMC (2019) were conducted from a UK NHS or PSS perspective, therefore the other six studies were considered less appropriate to inform the economic analysis. However, as the Lecat *et al.* (2019) study did not present cost and resource use data separately for the patient population of interest in this submission, it was not considered relevant to inform the economic analysis. Given that the cost inputs in the SMC submission of tisagenlecleucel (2019) were informed by sources such as the British National Formulary (BNF) at the time of the SMC submission, unit cost inputs were directly sourced from the NHS reference costs 2021–22, BNF and the electronic Marketing Information Tool (eMIT) to inform the model in this submission.[121-123] Resource use estimates were based on a number of sources including data from the ELIANA clinical trial (DCO 17th Nov 2022; unless otherwise stated), previous technology appraisals relevant to the submission and advice from clinical experts experienced in the treatment of patients aged up to 25 with r/r B-cell ALL in the UK consulted as part of the original submission (TA554) and the current submission.[4, 14, 58]

Specifically, the following cost components were considered in the model: pre-treatment costs for the tisagenlecleucel arm (leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy), drug acquisition costs for both the intervention and relevant comparators, associated outpatient administration costs, associated hospitalisation and ICU costs, AE costs, subsequent allo-SCT costs, follow-up and monitoring costs (by health state), and terminal care costs. In line with the accepted approach in the appraisal for brexucabtagene autoleucel in r/r ALL

in adult patients (TA893),[58] costs associated with treatment with tisagenlecleucel were modelled based on the NHS tariff for CAR-T therapies (see Section B.3.5.1 below for further details).

Overall, only direct medical costs were considered in the economic model from the NHS and PSS perspective and these are described in more detail below. In the absence of any additional sources of evidence, assumptions were made for cost/resource inputs included in the model where necessary and were validated through discussions with clinical experts.[14] With the exception of the use of the NHS CAR-T tariff, the modelling of costs and healthcare resource use in the current submission is largely aligned to the approach taken in the original appraisal (TA554) which was deemed to be generally appropriate by the ERG. As noted by the ERG in TA554, costs associated with training for health professionals for the delivery of tisagenlecleucel and its associated care was not included in the base case analysis. Given the current widespread use of CAR-T therapy as indicated by the clinicians consulted as part of this submission, the volume of such training requirements and its associated costs is expected to be limited. The inclusion of training costs as part of the NHS CAR-T tariff therefore represents a conservative approach to costs associated with tisagenlecleucel.

The impact on caregivers, whether they be formal caregivers or informal caregivers (e.g. parents of young children) is not considered in the analysis. Concerns on emotional, practical and financial impact experienced by caregivers of r/r B-cell ALL patients were raised by patient organisations in the original appraisal (TA554),[9] thereby highlighting the importance of its consideration. If such impact on caregivers were to be incorporated, it would be expected to benefit tisagenlecleucel in the analysis relative to the base case results presented.

B.3.5.1 Intervention and comparators' costs and resource use

Tisagenlecleucel

In the base case analysis, the administration of tisagenlecleucel, covering leukapheresis, treatment administration, treatment adverse events, monitoring and training is accounted for via an NHS tariff for treatment with CAR-T therapy. This tariff is in line with that agreed between the manufacturer, the external assessment group (EAG), the committee, and NHS England in the NICE appraisal for brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893).[58] This tariff amounts to £41,101 for treatment with tisagenlecleucel, in line with that used in TA893. This approach was chosen in order to align with NICE's most recently accepted costs for administering a CAR-T therapy, deemed appropriate for use to model costs associated with administration of CAR-T therapies. In line with feedback received from the CDF lead during the committee meeting for TA893, the costs for bridging chemotherapy drugs and its administration, allo-SCT and IVIg are applied separately.[58]

Whilst the committee in TA893 deemed the tariff of £41,101 to be appropriate, this remains an estimation of different costs, projected onto a single treatment. In order to explore uncertainty associated with this estimate, a scenario analysis was conducted in which the costs covered by the NHS tariff – leukapheresis, treatment administration, management of adverse events, monitoring and training – are costed individually, based on NHS reference costs. The costs included separately in this scenario are noted and described in full in the sections below.

Pre-treatment costs

As described in Section B.1.2, there are three pre-treatment phases that patients undergo prior to receiving infusion with tisagenlecleucel: leukapheresis, bridging chemotherapy and

lymphodepleting chemotherapy. The cost of leukapheresis is covered by the NHS tariff as mentioned above. The costs associated with each of these pre-treatment phases were applied in the first cycle of the model. The proportion of patients attributed the costs of each of the three pre-treatment phases form part of the decision tree component of the economic model structure and can all be user-modified within the economic model on the "Specification" tab.

- **Leukapheresis**: collection of T-cells from the patient (included in the NHS CAR-T tariff, and thus detailed costs described below were included in a scenario only). The cost of leukapheresis was estimated to be £2,575.70 based on NHS Reference Costs 2021-2022 (Elective Inpatient, SA43Z Leucopheresis).[122] All patients in the tisagenlecleucel arm of the economic model were assumed to incur the cost of leukapheresis, regardless of whether they received tisagenlecleucel or not.
- **Bridging chemotherapy:** to stabilise disease whilst waiting for tisagenlecleucel manufacturing and infusion (not included in the NHS CAR-T tariff; included in all analyses)

Within the tisagenlecleucel clinical trials, the provision of bridging chemotherapy was left to investigator discretion and therefore a wide range of bridging chemotherapy regimens were received by patients.[2] The cost of bridging chemotherapy was based on feedback from UK clinical experts consulted as part of the original submission (TA554), who stated that patients would typically receive bridging chemotherapy in the outpatient setting.[14] In the economic model, it was assumed that patients received the following bridging chemotherapy regimen in the outpatient setting for a total of 3 weeks, based on the current manufacturing time of tisagenlecleucel of 3 weeks. This assumption is in line with the approach taken and accepted by the ERG in the original appraisal (TA554) to be reflective of the bridging and lymphodepleting chemotherapy regimen in the UK.

- Allopurinol 100 mg/m^2 orally three times daily for five days
- Dexamethasone 6 mg/m^2/day for 14 days then dexamethasone 3 mg/m^2/day for seven days
- Vincristine 1.5 mg/m^2 IV weekly for three weeks
- Intrathecal methotrexate 12 mg on days one and eight
- Co-trimoxazole 480 mg orally twice daily for two consecutive days each week for three weeks

Drug costs for the above regimens were obtained from eMIT (2023).[121] The average dose required per administration was based on an average BSA of 1.25 m^2 (based on ELIANA [DCO 17th Nov 2022]).[2] Vial sharing was not considered. For oral therapies, patients were assumed to incur the costs of the minimum total number of packs required to cover the three-week treatment period. For IV and intrathecal administered therapies, patients were assumed to incur a daily cost of outpatient administration, which was based on NHS Reference Costs 2021-2022: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (for the first administration) and NHS Reference Costs 2021-2022: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (for subsequent administrations).[122] A summary of the costs associated with bridging chemotherapy are presented in Table 49 to Table 51.

The proportion of patients who received infusion with tisagenlecleucel that were assumed to receive bridging chemotherapy was 100% based on UK expert clinician feedback consulted as part of the original appraisal (TA554).[14] For patients who discontinued prior to tisagenlecleucel infusion due to manufacture failure/AEs or death, it was assumed that 50% of patients still received the full costs of bridging chemotherapy. It should be noted that the receipt of bridging chemotherapy in clinical practice is not mandatory and some patients may not require bridging chemotherapy.

- **Lymphodepleting chemotherapy:** to facilitate the engraftment and homeostatic expansion of tisagenlecleucel cells (not included in the NHS CAR-T tariff; included in all analyses)

As stated in the SmPC for tisagenlecleucel, it is recommended that patients receive lymphodepleting chemotherapy prior to infusion with tisagenlecleucel, unless the patient's WBC count is ≤1,000 cells/μL within one week prior to infusion.[10] Following the completion of lymphodepleting chemotherapy, it is recommended that patients are infused with tisagenlecleucel within 2–14 days.

The following lymphodepleting chemotherapy regimens are recommended in the SmPC and the cost of receiving each regimen was included within the economic model.[10]

- Fludarabine (30 mg/m^2 IV daily for four days) and cyclophosphamide (500 mg/m^2 IV daily for two days starting with the first dose of fludarabine); or
- Cytarabine (500 mg/m^2 IV daily for two days) and etoposide (150 mg/m^2 IV daily for three days starting with the first dose of cytarabine) *if the patient has experienced a previous grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemo-refractory state to a cyclophosphamide containing regimen administered shortly before lymphodepleting chemotherapy.*

It was assumed that 96% of patients who received infusion with tisagenlecleucel received lymphodepleting chemotherapy based on data from the ELIANA (DCO 25th Apr 2017) as this data was not available in the latest data cut-off of 17th Nov 2022.[67] For any patients who did not ultimately undergo tisagenlecleucel infusion (either due to manufacture failure/AEs or death), it was assumed that 50% of these patients receive lymphodepleting chemotherapy.

The proportion of patients receiving either Regimen 1 or Regimen 2 of lymphodepleting chemotherapy was based on the ELIANA trial (DCO 25th Apr 2017), within which 94.7% of patients received Regimen 1 and 1.3% of patients received Regimen 2.[67] These percentages were scaled up to 100% (i.e. 98.6% of patients were assumed to receive Regimen 1 and 1.4% of patients were assumed to receive Regimen 2) within the model.

Drug costs for the above regimens were obtained from eMIT.[121] The average dose required per administration was based on an average BSA of 1.25 m^2 (based on ELIANA [DCO 17th Nov 2022]).[2] Vial sharing was not considered. The proportion of patients receiving lymphodepleting chemotherapy in hospital was based on the analysis of hospitalisation data from the ELIANA trial (DCO 25th Apr 2017) where 65.8% of patients were associated with a length of hospitalisation stay of 13.98 days.[67] The average daily cost of hospitalisation was based on NHS Reference Costs 2021–2022 and the weighted average of Day Case, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more (PM40A, PM40B, PM40C).[122] This is a conservative estimate given the consensus amongst UK clinical experts consulted as part of the original submission (TA554), to validate the model assumptions, was that the length of hospitalisation stay for lymphodepleting chemotherapy observed within the ELIANA trial is likely to be overestimated; in clinical practice, patients would typically be in hospital for a maximum of 7 days with lymphodepleting chemotherapy prior to receiving tisagenlecleucel infusion.[14] The ERG considered the base case assumption for the modelling of the length of hospitalisation stay in the original appraisal (TA554) to be appropriate. Hence, this assumption was retained and the length of hospitalisation stay for lymphodepleting chemotherapy was informed by the data from the ELIANA trial.

The remaining 34.2% of patients were assumed to receive lymphodepleting chemotherapy in the outpatient setting and were associated with a daily cost of outpatient administration, which was based on NHS Reference Costs 2021–2022: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (for the first administration) and NHS Reference Costs 2021–2022: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (for subsequent administrations).[122] It was assumed that the receipt of more than one drug in one day would incur only one administration cost per day. A summary of the costs associated with lymphodepleting chemotherapy are presented in Table 49 to Table 51.

Table 49: Tisagenlecleucel pre-treatment costs (drug/procedure costs)

Cost of lymphodepleting regimen	Dose	Unit cost (£) (vial size)	Average dose per infusion (mg)	Number of vials per infusion/ packs per admin	Total number of infusions/ packs required	Drug cost per regimen (£)	Proportion receiving regimen	Total cost (£)	Source/ Assumptions
NHS CAR-T tariff (leukapheresis, tisagenlecleucel administration, adverse events, monitoring, training)								**£41,101.00**	
Leukapheresis[a]								**£2,575.70**	NHS Reference Costs 2021–2022: Elective Inpatient SA43Z Leukapheresis[122]
Bridging chemotherapy (drug costs)[b]								**£36.50**	
Allopurinol	100 mg/m^2 orally three times daily for five days	£0.32 (28 x 100 mg tablets)	124.57	1	1	£0.32	N/A	£0.32	eMIT 2023 (NPC Code: DJA084 Allopurinol 100 mg tablets/packsize 28)[121]
Dexamethasone	6 mg/m^2 orally for 14 days then tapered for seven days (assumed to receive three mg/m^2 daily during tapering)	£2.46 (50 x 2 mg tablets)	6.23	2	2	£4.91	N/A	£4.91	eMIT 2023 (NPC Code: DFN018 Dexamethasone 2 mg tablets/packsize 50)[121]
Vincristine	1.5 mg/m^2 IV weekly for three weeks	£8.34 (2 mg vial)	1.87	1	3	£25.02	N/A	£25.02	eMIT 2023 (NPC Code: DHA111 Vincristine 2 mg/2 ml solution for injection vials/packsize 5)[121]
Intrathecal methotrexate	12 mg intrathecally on days one and eight	£2.35 (50 mg vial)	12.00	1	2	£4.70	N/A	£4.70	eMIT 2023 (NPC Code: DHA038 Methotrexate 5 mg/2 ml solution for injection vials/packsize 5)[121]

Co-trimoxazole	480 mg orally twice daily on two consecutive days each week	£1.54 (28 x 480 mg tablets)	480.00	1	1	£1.54	N/A	£1.54	eMIT 2023 (NPC Code: DEA224 Co-trimoxazole 80 mg/400 mg tablets/packsize 28)[121]
Lymphodepleting chemotherapy[b]								**£92.37**	
Regimen 1 (drug costs)									
Fludarabine	30 mg/m2 IV daily for four doses	£16.66 (50 mg vial)	37.37	1	4	£93.11	98.61%	£91.81	eMIT 2023 (NPC Code: DHA377 Fludarabine phosphate 50 mg/2 ml solution for injection)[121]
Cyclophosphamide	500 mg/m2 IV daily for two doses	£13.23 (1000 mg vial)	622.86	1	2				eMIT 2023 (NPC Code: DHA014 Cyclophosphamide 1 g powder for solution for injection)[121]
Regimen 2 (drug costs)									
Cytarabine	500 mg/m2 IV daily for two days	£8.28 (1000 mg vial)	622.86	1	2	£40.22	1.39%	£0.56	eMIT 2023 (NPC Code: DHA020 Cytarabine 1 g/10 ml solution for injection)[121]
Etoposide	150 mg/m^2 IV daily for three days	£3.94 (100 mg vial)	186.86	2	3				eMIT 2023 (NPC Code: DHA320 Etoposide 100 mg/5 ml solution for injection)[121]

[a]Included in the NHS CAR-T tariff; included in scenario analysis only. [b]Not included in NHS CAR-T tariff; included in all analyses.
Note: The average dose required per administration is based on an average BSA of 1.25 m^2 (based on ELIANA [DCO 17th Nov 2022]).[2] Some unit costs are rounded to 2dp.
Abbreviations: eMIT: electronic market information tool; IV: intravenous; mg: milligrams; NPC: National Product Code.

Table 50: Tisagenlecleucel pre-treatment costs (outpatient administration costs)

Drug	Max. number of days of infusion	Total cost of outpatient administration	Proportion receiving each regimen	Proportion receiving outpatient administration	Total cost	Source/Assumptions
Bridging chemotherapy (outpatient administration costs)[a]					**£1,394.57**	
Vincristine (see dose above in Table 49)	3	£860.52	N/A	100%	£860.52	• Outpatient administration costs based on NHS Reference Costs 2021–2022: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (£208; for the first administration) and NHS Reference Costs 2021-2022: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (£326 for subsequent administrations). It was assumed that the receipt of more than one drug in one day would incur only one administration cost per day[122] • The proportion of patients receiving lymphodepleting chemotherapy in the outpatient setting was based on data from the ELIANA clinical trial (DCO 25th Apr 2017),[67] as these were not available in the most recent data cut for ELIANA (DCO 17th Nov 2022)
Intrathecal methotrexate (see dose above in Table 49)	2	£534.05	N/A	100%	£534.05	
Lymphodepleting chemotherapy (outpatient administration costs)[a]					**£404.52**	
Regimen 1 (see dose above in Table 49)	4	£1,186.98	98.6%	34.2%	£400.43	
Regimen 2 (see dose above in Table 49)	3	£860.52	1.4%		£4.09	

[a]Not included in NHS CAR-T tariff; included in all analyses.
Abbreviations: DCO: data cut-off; N/A: not applicable; NHS: National Health Service.

Table 51: Tisagenlecleucel pre-treatment costs (hospitalisation costs)

	Average daily cost of hospitalisation	Average length of hospitalisation (days)	Total cost of hospitalisation stay	Proportion receiving hospitalisation	Total cost	Source/Assumptions
Lymphodepleting chemotherapy (hospitalisation)[a]	£964.08	13.98	£13,477.84	65.8%	**£8,867.00**	• The proportion of patients receiving lymphodepleting chemotherapy administration in hospital was based on data from the ELIANA clinical trial (DCO 25th Apr 2017)[67] • The average daily cost of hospitalisation was based on NHS Reference Costs 2021–2022 and the weighted average of Day Case, Paediatric Acute Lymphoblastic Leukaemia with length of stay one day or more (PM40A, PM40B, PM40C).[122]

[a]Not included in NHS CAR-T tariff; included in all analyses.
Abbreviations: DCO: data cut-off; NHS: National Health Service.

Tisagenlecleucel infusion costs

As outlined above, all costs relating to the infusion of tisagenlecleucel were included as part of the NHS CAR-T tariff used in TA893.[58] Tisagenlecleucel infusion acquisition cost (including the cost of transportation, manufacture and delivery) is £282,000 at list price and £[redacted] at PAS price. All costs described below were explored separately as part of a scenario analysis.

The costs associated with the infusion of tisagenlecleucel within the scenario analysis included the acquisition cost of tisagenlecleucel, which includes transportation, manufacture and delivery, and the associated hospitalisation (including ICU) and outpatient administration costs (see Table 52). All costs were applied within the first cycle of the model. For paediatric and young adult patients with r/r B-cell ALL, tisagenlecleucel is recommended at the following doses (see the Summary of Product Characteristics in Appendix C):[10]

- For patients 50 kg and below: 0.2 to 5.0 x 10^6 CAR positive viable T cells/kg body weight
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based)

Based on data from the ELIANA trial (25th Apr 2017), 5.26% of patients received infusion with tisagenlecleucel in the outpatient setting; however, given the fact that it is more likely that 100% of patients would receive infusion with tisagenlecleucel in hospital in UK clinical practice, it was instead conservatively assumed that 0% of patients received infusion with tisagenlecleucel in the outpatient setting.[67] As such 100% of patients were assumed to incur an average length of hospitalisation stay of 25.85 days (based on data from the ELIANA trial [DCO 25th Apr 2017]), the cost of which was based on NHS Reference Costs 2021–2022 (Weighted average of Day Case, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more PM40A–PM40C) (see Table 52).[67, 122] It can be considered that the assumption of 25.85 days of hospitalisation stay following tisagenlecleucel is conservative, and that as clinicians become experienced in the delivery and management of tisagenlecleucel in the hospital setting, the length of hospitalisation stay may decrease for patients in the future.[14]

Finally, it was also assumed, based on data from the ELIANA trial (DCO 17th Nov 2022), that on average, patients receiving infusion with tisagenlecleucel would spend 1.74 days in ICU (not due to CRS) following infusion.[67] Whilst not all patients in the ELIANA trial had to be admitted to ICU, the median duration of ICU stay across all patients was adopted, an approach considered appropriate by the ERG and committee in TA554.[9] The average daily cost of ICU was estimated to be £3,110.65 based on NHS Reference Costs 2032–2022 and a weighted average of: Paediatric Critical Care [excluding transportation] XB01Z–XB07Z, XB09Z (see Table 52).[122]

Table 52: Infusion costs (and other hospitalisation costs) with tisagenlecleucel (scenario analysis)

Cost of infusion	Input	Source / Assumptions
Tisagenlecleucel infusion acquisition cost[a]	£282,000	The cost of tisagenlecleucel infusion includes the cost of transportation, manufacture and delivery.
Cost of hospitalisation (not ICU)	**Input**	**Source / Assumptions**
Proportion of patients requiring hospitalisation during or after infusion	100%	ELIANA (DCO 25th Apr 2017)[67]
Average length of hospitalisation stay (days)	25.85	ELIANA (DCO 25th Apr 2017)[67]

Average cost per day of hospitalisation	£964.08	Based on NHS Reference Costs 2021–2022 (Weighted average of Day Case, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more PM40A–PM40C)[122]
Total cost of hospitalisation	***£24,921.47***	Calculation
Cost of ICU (not due to CRS)	**Input**	**Source / Assumptions**
Average length of ICU stay (days)	1.74	ELIANA (DCO 17th Nov 2022)[2]
Average daily cost of ICU stay	£3,110.65	Based on NHS Reference Costs 2021-2022 (Weighted average of: Paediatric Critical Care [excluding transportation] XB01Z–XB07Z, XB09Z)[122]
Total cost of ICU stay	***£5,402.29***	Calculation
Total tisagenlecleucel infusion costs[a]	£312,323.77	**Calculation**

[a]Costs calculated are based on the list price of tisagenlecleucel. A simple confidential PAS of [redacted] exists.
Abbreviations: CRS: cytokine release syndrome; DCO: data cut-off; ICU: intensive care unit; NHS: National Health Service.

Blinatumomab

The costs associated with blinatumomab therapy included acquisition and outpatient administration costs as well as hospitalisation administration costs where necessary. It is acknowledged that a PAS exists for blinatumomab. In the absence of knowing the blinatumomab PAS discount, no PAS discount was assumed for blinatumomab in the base case analysis but the option to include a discount has been included within the economic model.

The dose of blinatumomab for patients up to the age of 18 was based on the dosing schedule used in the study by von Stackelberg *et al.* (2016):[7]

- Cycle 1 (four weeks followed by a two-week treatment-free interval):
  - Days 1–7: 5 µg/m^2/day
  - Days 8–28: 15 µg/m^2/day
- Cycle 2 and subsequent cycles (four weeks followed by a two-week treatment-free interval):
  - Days 1–28: 15 µg/m^2/day

The average dose required per infusion was based on an average BSA of 1.17 m^2 for patients <18 years (based on the ELIANA [DCO 17th Nov 2022]).[2] It is acknowledged that patients over the age of 18 years would receive a higher adult dose of blinatumomab in clinical practice and therefore the adjusted dosing for adults was incorporated into the economic model for the proportion of patients estimated to be over the age of 18 (and under the age of 25) with r/r B-cell ALL based on the ELIANA trial (17.7%; DCO 17th Nov 2022).[2] The dose of blinatumomab for patients over the age of 18 was based on the blinatumomab SmPC.[55]

- Cycle 1 (four weeks followed by a two-week treatment-free interval):
  - Days 1–7: 9 µg/day
  - Days 8–28: 28 µg/day
- Cycle 2 and subsequent cycles (four weeks followed by a two-week treatment-free interval):
  - Days 1–28: 28 µg/day

Vial sharing was not considered, based on feedback from UK clinical experts that vial sharing does not currently occur with blinatumomab in UK clinical practice, and thus costs were unchanged between paediatric and adult patients.[14]

Hospitalisation costs were applied in accordance with the requirements specified in the SmPC for blinatumomab, which recommends hospitalisation for the initiation of therapy for a minimum of 9 days in Cycle 1 and 2 days in Cycle 2.[55] Therefore, patients were assumed to be in hospital for 11 days total, after which they were assumed to receive blinatumomab in the outpatient setting. The average cost per inpatient day of blinatumomab administration was assumed to be the same as the average daily cost of hospitalisation for all therapies included within the economic model and was £964.08, based on NHS Reference Costs 2021–2022 (Weighted average of Day Case, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more PM40A–PM40C).[122] Patients receiving blinatumomab in the outpatient setting were assumed to incur a daily outpatient administration cost of £330.85, which includes the cost of chemotherapy delivery (£326.46) based on NHS Reference Costs 2021–2022 (Chemotherapy, Outpatient, SB15Z, Deliver Subsequent Elements of a Chemotherapy Cycle) as well as a daily pump set-up cost of £4.38 (inflated from 2014–2015 to 2021–2022 from the cost used in TA450, based on input from UK oncology nurses considering the pump to be a BodyGuard 323™ Ambulatory Infusion Pump).[53, 122]

The percentage of patients starting and completing each cycle of blinatumomab was based on treatment exposure data from the study by von Stackelberg *et al.* (2016) and, in the absence of the appropriate data for the adult population, was assumed to be the same for patients receiving either the paediatric or adult dosing regimen.[7] The total costs of blinatumomab included in the economic analysis are summarised in Table 53, and were applied in the first cycle of the model. Whilst this is a simplifying approach, the maximum number of 6-week cycles of blinatumomab typically received is 2; therefore, treatment with blinatumomab is not anticipated to extend beyond one year and hence discounting is not affected. This is in line with committee preference in the original submission for tisagenlecleucel in this indication (TA554).[1]

Salvage chemotherapy (FLAG-IDA)

As discussed previously within the submission, feedback from UK clinical experts was that if they were to use salvage chemotherapy for 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 chemotherapy regimen of choice would be FLAG-IDA (fludarabine, cytarabine and idarubicin).[4] As such, the costs of salvage chemotherapy within the model were based on the drug acquisition and administration costs associated with treatment with the FLAG-IDA regimen.

The dosing regimen of FLAG-IDA was based on a protocol from the NHS Network Site Specific Group and validated with UK clinical experts and comprised 1 cycle of:[14, 124]

- Fludarabine 30 mg/m^2 daily for five doses;
- Cytarabine 2 g/m^2 daily for five doses;
- Idarubicin 8 mg/m^2 daily for three doses;
- Granulocyte colony stimulating factor (G-CSF) 5 µg/kg daily for 12 doses.

Feedback from UK clinical experts was that the FLAG-IDA regimen would always be given as an inpatient in hospital i.e. there would be no outpatient administration, and patients would typically stay in hospital for at least 3–4 weeks following completion of the therapy.[14] As such, and in the absence of any clinical trial data to suggest otherwise, it was conservatively assumed that all administration costs would be covered by the daily cost of hospitalisation and that patients would

remain in hospital for 21 days, in line with the approach accepted by the committee in TA554. A summary of the costs associated with salvage chemotherapy (FLAG-IDA) is presented in Table 54.

Table 53: Blinatumomab drug costs

Cycle	Cost per vial	Dose	Average dose per infusion	No. of vials per infusion	No. of infusions per cycle	Distribution of patients per cycle	Total drug cost	Source/Assumptions
Cycle 1 (days 1–7)	£2,017.00 (38.5 mcg)	5 µg/m^2/day[a]	5.84	1.00	7	96%	£54,055.60	• The cost per vial of blinatumomab is derived from the BNF Online[145] • The dosing schedule and the percentage of patients starting and completing each cycle of blinatumomab are based on treatment exposure data from the study by von Stackelberg *et al.* (2016)[7] • The average dose required per infusion for the paediatric population (<18 years) is based on an average BSA of 1.17 m^2 based on ELIANA [DCO 17th Nov 2022])[2] • The average dose required per infusion for the adult population (>18 years) is independent of the patient BSA. Vial sharing was not considered and thus costs were unchanged between paediatric and adult patients
		9 µg/d[b]	9.0[b]					
Cycle 1 (days 8–28)	£2,017.00 (38.5 mcg)	15 µg/m^2/day[a]	17.51	1.00	21			
		28 µg/d[b]	28.0[b]					
Cycle 2 (days 1–28)	£2,017.00 (38.5 mcg)	15 µg/m^2/day[a]	17.51	1.00	28	31%	£17,749.60	
		28 µg/d[b]	28.0[b]					
Total cost							**£71,805.20**	

Note: given no vial sharing was assumed, the same number of vials are required for both paediatric and adult patients hence the costs are the same. [a]Dose for paediatric patients (<18 years) [b]Dose for adult patients (≥18 years)
Abbreviations: BNF: British National Formulary; BSA: body surface area.
Source: BNF Online;[145] ELIANA [DCO 17th Nov 2022]);[2] von Stackelberg *et al.* (2016).[7]

Table 54: Salvage chemotherapy (FLAG-IDA) drug costs

Treatment	Cost per vial	Dose	Average dose per infusion	No. of vials per infusion	No. of infusions per cycle	Total drug cost	Source/Assumptions
Fludarabine	£16.66 (50 mg)	30 mg/m^2 daily	37.37 mg	1	5	£83.30	• The cost per vial of fludarabine and cytarabine are derived from the Drugs and pharmaceutical eMIT[121] • The cost per vial of idarubicin is derived from the BNF Online[146] • The dosing schedules are based on a protocol from the NSSG and validated with UK clinical experts[14, 124] • The average dose required per infusion is based on an average BSA of 1.25 m^2 on ELIANA [DCO 17th Nov 2022])[2]
Cytarabine	£8.28 (1000 mg)	2 g/m^2 daily	2,491.43 mg	3	5	£124.27	
Idarubicin	£87.36 (5 mg)	8 mg/m^2 daily	9.97 mg	3	3	£524.16	
G-CSF	£56.84 (600 mg)	5 µg/kg daily	6.23 mg	1	12	£682.08	
Total cost						**£1,413.82**	

Abbreviations: BNF: British National Formulary; BSA: body surface area; eMIT: electronic market information tool; FLAG-IDA: fludarabine, cytarabine, idarubicin and G-CSF; G-CSF: granulocyte colony stimulating factor; mg: milligram; NHS: National Health Service; NSSG: NHS Network Site Specific Group; UK: United Kingdom.
Source: eMIT;[121] BNF Online;[146] ELIANA [DCO 17th Nov 2022]);[2] UK clinical expert opinions.[14, 124]

Subsequent therapies: subsequent allo-SCT

The economic analysis assumed that patients could receive a subsequent allo-SCT after initial treatment. No other subsequent therapies were considered as feedback from UK clinical experts was that following a further relapse in this setting, patients would be unlikely to receive further active therapy and any treatment would be palliative in nature.

The rates of subsequent allo-SCT were obtained from the same clinical source used for the efficacy inputs and were presented previously in Table 33. A scenario based on real-world use of tisagenlecleucel during the managed access period is also explored.[3] In this scenario, 12.28% of patients are modelled as receiving a subsequent SCT following treatment with tisagenlecleucel.[3]

The costs and disutility associated with undergoing a subsequent allo-SCT were added separately for the proportion of patients assumed to receive a subsequent allo-SCT following each treatment. The costs associated with a subsequent allo-SCT were considered in three parts: stem cell harvesting, the cost of the procedure, and the cost of long-term follow-up (Table 55). The stem cell harvesting and allo-SCT procedure costs were based on NHS Reference Costs 2021–2022.[122] Since only the cost of stem cell harvesting and the cost of the allo-SCT could be sourced from NHS reference costs, the costs associated with the long-term follow-up of an allo-SCT were costed separately, based on the post-transplantation estimates from a UK Stem Cell Strategy Oversight Committee Report published in 2014.[147] The follow-up cost input was weighted by the proportion of patients who remained alive at different time periods (i.e. 6 months, 12 months, and 24 months) post the allo-SCT procedure, and the total cost was inflated from 2012–2013 costs to 2021–2022 costs using the hospital and community health services (HCHS) index.[148]

Table 55: Subsequent allo-SCT costs

Component	Cost	Source
Stem cell harvesting cost	£5,441.44	NHS Reference Costs 2021–2022: Weighted average of Elective Inpatient SA18Z Bone marrow harvest and SA34Z Peripheral Blood Stem Cell Harvest[122]
Allo-SCT procedure	£102,040.46	NHS Reference Costs 2021–2022: Weighted average of Elective Inpatient Paediatric Bone Marrow Transplant and Peripheral Blood Stem Cell Transplant (SA20B–SA23B, SA38B, SA39B)[122]
Allo-SCT follow-up cost (up to 24 months post allo-SCT)	£43,745.53	UK Stem Cell Strategy Oversight Committee (see detailed calculation in Table 56)[147]
Total cost	**£151,227.43**	

Abbreviations: allo-SCT: allogeneic stem cell transplantation; NHS: National Health Service; UK: United Kingdom.

Table 56: Subsequent allo-SCT follow-up cost breakdown

Component	Cost	% alive	Weighted cost
Follow-up 1 (up to 6 months)	£28,390	90%	£25,551
Follow-up 2 (6 to 12 months)	£19,502	48%	£9,361
Follow-up 3 (12 to 24 months)	£14,073	31%	£4,363
Total cost (2012/2013 cost year)			£39,275.00
Total cost (2021/2022 cost year)[a]			**£43,745.53**

[a]Total cost in 2021/2022 cost-year was inflated from total cost in 2012/2013 cost year.
Abbreviations: allo-SCT: allogeneic haematopoietic stem cell transplantation; UK: United Kingdom.
Source: UK Stem Cell Strategy Oversight Committee.[147]

B.3.5.2 Health-state unit costs and resource use

Monitoring and follow-up costs

Monitoring and follow-up costs consisted of outpatient consultant visits and any relevant clinical tests or procedures (e.g. full blood count, electrocardiogram, and bone marrow biopsy). The costs of visits and tests for patients receiving tisagenlecleucel were included in the NHS CAR-T tariff.

The frequency of monitoring and follow-up were assumed to vary by treatment, health state, and the time horizon and were validated by UK clinical experts in the original appraisal, and noted as appropriate by the EAG.[9, 14] Since the long-term follow-up costs for patients receiving a subsequent allo-SCT were assumed to cover all relevant follow-up costs for these patients, the proportion of patients receiving subsequent allo-SCT were not assumed to receive any further monitoring and follow-up costs as described in this section. The follow-up schedules and unit costs are described in Table 57 and Table 58. Table 59 summarises the follow-up costs for all therapies by health state and follow-up year.

For patients receiving salvage chemotherapy (FLAG-IDA) and blinatumomab who remained in the EFS state, the frequency of monitoring and follow-up was obtained from the National Comprehensive Cancer Network (NCCN) guideline.[149] For patients receiving tisagenlecleucel who remain in the EFS state, the frequency of monitoring and follow-up was derived from the ELIANA trial protocol.[80] In the PD health state, the frequency of monitoring and follow-up was assumed to be the same for all patients, regardless of the therapy received, and was assumed to be the same as that in the EFS state of blinatumomab and salvage chemotherapy (FLAG-IDA) during Year 1, an approach considered appropriate by the EAG in TA554.[9] For any patients remaining alive in the EFS state after 5 years, monitoring and follow-up costs were assumed to be the same (based on the year 5+ EFS resource use for the comparators), regardless of the therapy received, and regardless of the health state patients were in. The unit costs of the specific tests and services were based on NHS Reference 2021–2022 and the BNF.[122, 123]

Table 57: Follow-up schedule and unit cost inputs for patients in the EFS health state

Item	Unit cost	Yearly frequency (Year 1)[a]	Yearly frequency (Year 2)[a]	Yearly frequency (Years 3-5)[a]	Yearly frequency (Years 5+)[a]	Source / Assumptions
Tisagenlecleucel						
Consultant visit	£329.62	12	4	2	1	NHS Reference Costs 2021–2022: Consultant Led, WF01A–260, Paediatric Medical Oncology[122]
Haematology panel	£2.96	16	4	2	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS05, Haematology[122]
Coagulation panel	£2.39	3	0	0	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[122]
Chemistry panel (including liver function test)	£1.55	16	4	2	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[122]
CSF	£380.54	1	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, HC72B–421, Paediatrics[122]
Serum test	£2.39	5	0	0	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[122]
B-cell and T-cell test	£2.96	8	2	2	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS05, Haematology[122]
ECG	£244.81	1	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, EY51Z-303, Clinical Haematology[122]
Bone marrow aspirate	£518.88	3	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, SA33Z–303, Clinical Haematology[122]
Bone marrow biopsy	£518.88	3	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, SA33Z–303, Clinical Haematology[122]
Blinatumomab and salvage chemotherapy (FLAG-IDA)						
Consultant visit	£329.62	6	4	2	1	NHS Reference Costs 2021–2022: Consultant Led, WF01A–260, Paediatric Medical Oncology[122]
Haematology panel	£2.96	6	4	2	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS05, Haematology[122]

CSF	£380.54	1	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, HC72B–421, Paediatrics[122]
Bone marrow aspirate	£518.88	1	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, SA33Z–303, Clinical Haematology[122]
Echocardiogram	£251.86	1	0	0	0	NHS Reference Costs 2021–2022: Outpatient Procedures, EY50Z–303, Clinical Haematology[122]
Liver function test	£1.55	6	0	0	0	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[122]

[a]Follow up frequencies for tisagenlecleucel were derived from ELIANA.[2] Follow up frequencies for chemotherapy regimens and service items were based on NCCN guidelines.[149]
Abbreviations: CSF: cerebrospinal fluid; ECG: electrocardiogram; NHS: National Health Service.

Table 58: Follow-up schedule and unit cost inputs for patients in the PD health state

Parameter	Unit cost	Yearly frequency[a]	Source
Consultant visit	£329.62	6	NHS Reference Costs 2021–2022: Consultant Led, WF01A–260, Paediatric Medical Oncology[122]
Haematology panel	£2.96	6	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS05, Haematology[122]
CSF	£380.54	1	NHS Reference Costs 2021–2022: Outpatient Procedures, HC72B–421, Paediatrics[122]
Bone marrow aspirate	£518.88	1	NHS Reference Costs 2021–2022: Outpatient Procedures, SA33Z–303, Clinical Haematology[122]
Echocardiogram	£251.86	1	NHS Reference Costs 2021–2022: Outpatient Procedures, EY50Z–303, Clinical Haematology[122]
Liver function test	£1.55	6	NHS Reference Costs 2021–2022: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[122]

[a]The test frequencies are assumed to be the same as first year follow-up frequency based on the UK-specific Leukaemia and Lymphoma Research guideline.[150]
Abbreviations: CSF: cerebrospinal fluid; ECG: electrocardiogram; NHS: National Health Service.

Table 59: Follow-up cost inputs summary (monthly cost by treatment)

Health state and year	Tisagenlecleucel	Salvage chemotherapy	Blinatumomab
EFS (year 1)	£472.58[a]	£263.00	£263.00
EFS (year 2)	£111.87	£110.86	£110.86
EFS (year 3–5)	£56.18	£55.43	£55.43
EFS (post 5 years)	£27.47	£27.47	£27.47
PD (year 1)	£191.00[a]	£263.00	£263.00
PD (post year 1)	£263.00	£263.00	£263.00
Long-term survivors (EFS and PD)	£27.47	£27.47	£27.47

[a]Costs calculated after applying NHS tariff which covers follow-up costs for the first 100 days after infusion.
Abbreviations: EFS: event-free survival; PD: progressive disease.
Source: ELIANA trial protocol;[80] Leukaemia and Lymphoma research guideline;[150] NCCN guidelines;[149] NHS Reference Costs 2021–2022.[122]

Terminal care costs

All patients who die in the economic model prior to 5 years were assumed to incur a one-time terminal care cost which was applied during the cycle prior to patient death. Given patients who survive beyond 5 years are considered long-term survivors, it was assumed that these patients would not incur the costs of terminal care. This is in line with the blinatumomab adult appraisal, within which only patients who died within 48 months received the cost of terminal care, and was accepted in the original appraisal (TA554).[9, 151] The cost of terminal care was assumed to be £13,198.42, based on a weighted average of NHS Reference Costs 2021–2022 Non-Elective Long Stay Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more (PM40A–PM40C).[122]

B.3.5.3 Adverse reaction unit costs and resource use

Where data were available, any grade 3 or 4 AEs regardless of study-drug relationship that occurred in ≥5% of patients were included in the economic model. Consistent with the patient baseline characteristics and clinical efficacy inputs of the base case analysis, AE rates for tisagenlecleucel were derived from the patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=79) in ELIANA (DCO 17th Nov 2022), however were only accounted for in a scenario analysis in which cost of AEs were not modelled using the NHS CAR-T tariff.[2] For blinatumomab, AE rates were derived from von Stackelberg *et al.* (2016). For salvage chemotherapy (FLAG-IDA), in the absence of any clinical evidence for FLAG-IDA, the AE rates from Jeha *et al.* (2006) were used.[7, 8] The costs associated with the treatment of each AE were derived from NHS Reference Costs 2021–2022.[122]

The rates and unit costs of the AEs included within the economic model are presented in Table 62.

CRS and B-cell aplasia

As CRS is an AE that is specific to treatment with tisagenlecleucel and blinatumomab, and could be associated with substantial resource use, a more detailed calculation of the costs associated with the treatment of grade 3 or 4 CRS was performed. CRS event costs were calculated as the sum of the average ICU admission cost together with the cost of tocilizumab acquisition and were applied to the proportion of patients experiencing grade 3 or 4 CRS in the ELIANA (DCO 17th Nov 2022) and von Stackelberg *et al.* (2016).[2, 7]

The average length of ICU stay was estimated to be 11.10 days, based on ELIANA trial data. The average daily cost per ICU stay was based on NHS Reference Costs 2021–2022 and a weighted average of Paediatric Critical Care (XB01Z-XB07Z, XB09Z).[122] The detailed resource use inputs considered in the CRS AE cost estimation are listed in Table 60. A scenario analysis was explored in which the average length of ICU stay due to CRS was assumed to be three days. This was in light of feedback from UK clinicians that the length of ICU stay reported in the ELIANA trial may not reflect UK practice, in which ICU stay for CRS would be lower. ICU stay due to reasons other than CRS were adjusted accordingly, from 1.74 days in the base case to 1.54 days in this scenario analysis.

Given the fact that a confidential PAS is available for tocilizumab, a scenario analysis was performed to explore the effect of this, with an estimated PAS of 20% (in the absence of knowing the tocilizumab PAS discount).

Table 60: Detailed resource use inputs for CRS cost estimation

Parameter	Daily ICU cost/unit cost per infusion	Duration (days)/number of doses	Total cost per CRS event
CRS cost per event			**£35,142.62**
Paediatric ICU admission	£3,110.65	11.10 days	£34,528.22
Tocilizumab treatment	£496.75	1.24 doses	£614.40

Abbreviations: CRS: cytokine release syndrome; ICU: intensive care unit.
Source: ELIANA CSR (17th Nov 2022);[2] Novartis Data on File.[4]

In addition to CRS, the model also considered the cost of B-cell aplasia in more detail. B-cell aplasia is a common condition for patients treated with tisagenlecleucel and intravenous immunoglobulin (IVIg) is typically prescribed for patients for symptom management. The model

considered 73.33% of patients with tisagenlecleucel infusion would experience hypogammaglobulinaemia, based on ELIANA trial data (DCO 17th Nov 2022) and the median time to B-cell recovery was assumed equal to the median treatment duration (11.4 months), based on clinical expert feedback.[2, 4] Clinical feedback further noted that only 75% of patients of experiencing hypogammaglobulinaemia would receive IVIg in NHS practice, which was included in the calculation of the total number of patients receiving IVIg in the model. This aligns with prior committee preference in TA554, which noted that treatment with IVIg may have been overestimated in the original company submission.[1] A scenario analysis was also explored in which all patients experiencing hypogammaglobulinaemia receive IVIg. Noting that patients receiving blinatumomab treatment may also experience hypogammaglobulinaemia and therefore receive IVIg, this was also explored in a scenario analysis (see Section B.3.10.3). The total monthly drug cost of IVIg was calculated based on a dosing schedule obtained from the NICE mock appraisal and respective unit costs obtained from the BNF 2023.[123, 152]

A monthly outpatient administration cost was included and was based on NHS Reference Costs 2021–2022 Chemotherapy, SB12Z, Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance.[122] The total IVIg cost was calculated to be £11,176.85 based on the proportion of patients receiving IVIg and the average treatment duration, and was applied as a one-time cost in the model. Table 61 presents the detailed dosing and unit costs for B-cell aplasia.

Table 61: Associated AE costs for B-cell aplasia

Item	Cost per package or vial, package size	Dosing schedule	Total drug cost per month	Total administration cost per month[a]	Duration	Proportion of patients[b]	Total IVIg cost
IVIg drug cost							
IVIg	£700.00 10,000 mg	500 mg/kg every month	£1,575.00	£207.59	11.4 months	55%	**£11,176.85**
IVIg	£175.00 2,500 mg						

[a]The model considered one infusion per cycle in the calculation of total administration cost per cycle.

[b]The model considered 73.33% of patients with tisagenlecleucel infusion would experience hypogammaglobulinaemia, based on ELIANA trial data (DCO 17th Nov 2022) and clinical feedback further noted that only 75% of patients of experiencing hypogammaglobulinaemia would receive IVIg in NHS practice.[2, 4]
Abbreviations: DCO: data cut-off; IVIg: intravenous immunoglobulin.
Source: BNF 2023 (IVIg);[152] ELIANA CSR (DCO 17th Nov 2022).[2]

Table 62: Rates and unit costs of the AEs included in the economic model

AEs	Tisagenlecleucel	Salvage chemotherapy	Blinatumomab	Unit cost	Source/Assumptions
Source for AE rates	ELIANA CSR (DCO 17th Nov 2022)[a,2]	Jeha *et al.* (2006)[b,8]	von Stackelberg *et al.* (2016)[c,7]		
Acute kidney injury	10.13%	-	-	£1,673.83	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Renal Disease with Renal Failure (PL38A–PL38C)[122]
Alanine aminotransferase increased	8.86%	-	15.71%	£409.24	NHS Reference Costs 2021–2022: Day Case Liver Failure Disorders without Interventions (GC01F)[122]
Anaemia	11.39%	-	35.71%	£368.84	NHS Reference Costs 2021–2022: Weighted average of Day Case Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (SA01G–SA01K), Haemolytic Anaemia (SA03G–SA03H), Iron Deficiency Anaemia (SA04G–SA04L) and Megaloblastic Anaemia (SA05G–SA05J)[122]
Anorexia	-	19.67%	-	£625.37	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Eating Disorders (PT53A–PT53B)[122]
Aspartate aminotransferase increased	13.92%	-	11.43%	£409.24	NHS Reference Costs 2021–2022: Day Case Liver Failure Disorders without Interventions (GC01F)[122]
Bacteraemia	2.53%	13.11%	-	£456.64	NHS Reference Costs 2021–2022: Weighted average of Sepsis without Interventions (WJ06G–WJ06J)[122]
Blood bilirubin increased	11.39%	-	-	£732.39	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric, Hepatobiliary or Pancreatic Disorders (PG71A–PG71C)[122]
CRS	48.10%	-	5.71%	£35,142.62	(See Table 60)
Decreased appetite	15.19%	-	-	£625.37	Cost of decreased appetite is assumed to equal the cost of anorexia[122]

Dermatitis	-	11.48%	-	£607.16	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric, Rash or Other Non-Specific Skin Eruption (PJ66A–PJ66C)[122]
Diarrhoea	2.53%	13.11%	-	£643.90	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Other Gastrointestinal Disorders (PF26A– PF26C)[122]
Encephalopathy	5.06%	-	-	£513.09	NHS Reference Costs 2021–2022: Weighted average of Day Case Cerebrovascular Accident, Nervous System Infections or Encephalopathy (AA22C–AA22G)[122]
Epistaxis	1.27%	13.11%	-	£2,937.95	NHS Reference Costs 2021–2022: Day Case Major Treatment of Epistaxis (CA12Z)[122]
Febrile neutropenia	34.18%	49.18%	17.14%	£529.09	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Febrile Neutropenia with Malignancy (PM45A–PM45D)[122]
Hallucination	-	13.11%	-	£282.85	NHS Reference Costs 2021–2022: Day Case Schizophrenia, Schizotypal or Delusional Disorders, treated by a Non-Specialist Mental Health Service Provider (WD07Z)[122]
Hepatomegaly	1.27%	11.48%	-	£388.08	NHS Reference Costs 2021–2022: Weighted average of Day Case Liver Failure Disorders without Interventions (GC01E–GC01F)[122]
Hypoglycaemia	6.33%	-	-	£390.03	NHS Reference Costs 2021–2022: Weighted average of Diabetes with Hyperglycaemic Disorders (KB02G-KB02K)[122]
Hypertension	6.33%	9.84%	5.71%	£390.85	NHS Reference Costs 2021–2022: Day Case Hypertension (EB04Z)[122]
Hypocalcaemia	6.33%	-	-	£384.92	NHS Reference Costs 2021–2022: Weighted average of Day Case Fluid or Electrolyte Disorders (KC05G–KC05H), with Interventions and Fluid or Electrolyte Disorders, without Interventions (KC05J–KC05N)[122]

Hypogamma-globulinaemia	7.59%	-	-	£384.92	Cost of hypogammaglobulinaemia is assumed to equal the cost of hypocalcaemia
Hypokalaemia	13.92%	-	17.14%	£384.92	Cost of hypokalaemia is assumed to equal the cost of hypocalcaemia
Hypophosphataemia	11.39%	-	-	£384.92	Cost of hypophosphatemia is assumed to equal the cost of hypocalcaemia
Hypotension	20.25%	18.03%	-	£390.85	Cost of hypotension is assumed to equal the cost of hypertension
Hypoxia	20.25%	-	-	£575.45	Cost of hypoxia is assumed to equal the cost of respiratory distress/failure
Infection	49.37%	9.84%	-	£770.54	NHS Reference Costs 2021–2022: Weighted average of Paediatric Major Infections (PW16A–PW16E)[122]
Leukopenia	2.53%	-	10.00%	£384.82	NHS Reference Costs 2021–2022: Weighted average of Day Case Agranulocytosis (SA35A–SA35E)[122]
Lymphocyte count decreased	18.99%	-	-	£384.82	Cost of lymphocyte count decreased is assumed to equal the cost of leukopenia
Nausea	2.53%	16.39%	-	£650.11	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric, Feeding Difficulties or Vomiting (PF28A–PF28E)[122]
Neutropenia	11.39%	14.75%	17.14%	£384.82	Cost of neutropenia is assumed to equal the cost of leukopenia
Neutrophil count decreased	26.58%	-	12.86%	£384.82	Cost of neutrophil count decreased is assumed to equal the cost of leukopenia
Petechiae	-	11.48%	-	£446.28	Cost of petechiae is assumed to equal the cost of coagulopathy
Platelet count decreased	18.99%	-	14.29%	£381.27	NHS Reference Costs 2021–2022: Weighted average of Day Case Thrombocytopenia (SA12G–SA12K)[122]
Pleural effusion	3.80%	9.84%	-	£599.27	Cost of pleural effusion is assumed to equal the cost of pulmonary oedema

Pneumonia	5.06%	9.84%	-	£634.36	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis (PD14A–PD14F)[122]
Pulmonary oedema	8.86%	-	-	£599.27	NHS Reference Costs 2021–2022: Weighted average of Day Case Pulmonary Oedema with Interventions (DZ20D) and Pulmonary Oedema without Interventions (DZ20E–DZ20F)[122]
Pyrexia	13.92%	14.75%	14.29%	£622.53	NHS Reference Costs 2021–2022: Weighted average of Day Case Paediatric Fever of Unknown Origin (PW20A–PW20C)[122]
Respiratory distress	1.27%	11.48%	-	£575.45	NHS Reference Costs 2021–2022: Weighted average of Day Case Respiratory Failure without Interventions (DZ27S–DZ27U)[122]
Sepsis	3.80%	13.11%	-	£456.64	NHS Reference Costs 2021–2022: Weighted average of Day Case Sepsis without Interventions (WJ06G–WJ06J)[122]
Thrombocytopenia	11.39%	-	21.43%	£381.27	NHS Reference Costs 2021–2022: Weighted average of Day Case Thrombocytopenia (SA12G–SA12K)[122]
White blood cell count decreased	21.52%	-	10.00%	£384.82	Cost of WBC count decreased is assumed to equal the cost of leukopenia
Total AE Costs	**£0.00[d]**	**£1,802.56**	**£2,847.49**		

Note: For transparency, AEs have been listed according to how the AE is reported in the relevant source. As such, some AEs may appear to be listed twice, but have been assumed to incur the same cost.

[a]Based on grade 3 or 4 AEs, regardless of study drug relationship, occurring any time post tisagenlecleucel infusion in >5% patients.[2]

[b]Based on grade ≥3 AEs, regardless of causality that occurred in ≥10% of patients in all cycles.[8]

[c]Based on AEs of worst grade ≥3 regardless of relationship to treatment that occurred in ≥5% of patients (who received the recommended dose of 5/15 μg/m^2/day in phase I or II) during the treatment period and until 30 days after the last treatment or before allo-SCT or start of chemotherapy.[7]

[d]Included in NHS tariff.

Abbreviations: AE: adverse event; allo-SCT: allogeneic stem cell transplantation; BNF: British National Formulary; CRS: cytokine release syndrome; DCO: data cut-off; ICU: intensive care unit; IVIg: intravenous immunoglobulin; NHS: National Health Service; WBC: white blood cell.

Source: ELIANA CSR (DCO 17th Nov 2022);[2] Jeha *et al.* (2006);[8] von Stackelberg *et al.* (2016).[7]

B.3.5.4 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model that have not already been listed above.

B.3.6 *Severity*

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider *et al*. (2022).[153] The total life expectancy for the modelled population was calculated using population mortality data from the Office for National Statistics for 2018–2020.[154] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al*. (2022) through the NICE DSU.[155]

The total QALYs for the current UK r/r B-cell ALL population on salvage chemotherapy and blinatumomab were calculated from Jeha *et al.* (2006)[8] and von Stackelberg *et al.* (2016)[8] studies, respectively. The absolute QALY shortfall and proportional QALY shortfall compared to the population receiving treatment with salvage chemotherapy and blinatumomab were above the threshold of 18, therefore, a severity modifier of 1.7 should be considered for base case results for this comparison.

It should be noted that the total QALYs calculated for the patients with r/r B-cell ALL receiving blinatumomab and salvage chemotherapy treatment are skewed given the use of mixture cure models to model survival. These models predict a small proportion of patients who receive allo-SCT and achieve cure (11.4% and 9.4% cure fractions for blinatumomab and salvage chemotherapy [FLAG-IDA], respectively). However, the majority of patients are expected to not be eligible for subsequent allo-SCT and thus have dismal prognosis, with no curative treatment options in a world where tisagenlecleucel is unavailable. The young age of the patient population included in the ELIANA, in which the mean age was 12 years upon trial entry, presents a compelling case to consider the application of a severity modifier to accurately assess the benefits of a disease affecting a young patient population with a high unmet need.

Table 63: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Percentage female	43.04%	Section B.3.3.1
Starting age	12.00	

Abbreviations: QALY: quality-adjusted life year.
Source: ELIANA CSR (17th Nov 2022).[2]

Table 64: Summary of QALY shortfall analysis

Treatment	Expected total QALEs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute Shortfall (AS)	Proportional Shortfall (PS)	Severity modifier vs comparator
Blinatumomab	23.79	3.06	20.73	0.87	1.7
Salvage chemotherapy		2.22	21.56	0.91	1.7

Abbreviations: AS: absolute shortfall; PS: proportional shortfall; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year.
Source: ELIANA CSR (17th Nov 2022);[2] von Stackelberg *et al.* (2016)[7]; Jeha *et al.* (2006).[8]

B.3.7 *Uncertainty*

The lack of randomised efficacy evidence comparing tisagenlecleucel with the identified relevant comparators leads to uncertainties in the clinical inputs informing the economic model, as noted in the original appraisal (TA554).[9] Efficacy data informing the model is instead based on naïve comparisons between sources. As discussed in Section B.2.9, MAICs were conducted based on IPD from ELIANA, and summary data from von Stackelberg *et al.* (2016) for blinatumomab and Jeha *et al.* (2006) for salvage chemotherapy (FLAG-IDA), based on the NICE DSU TSD 18 guidance.[7, 8, 156, 157] Given there were differences between tisagenlecleucel trials and that data with long-term follow-up from the ELIANA trial are now available, pooled data were not considered for inclusion in the base case MAICs or the economic model. This data are however, shown in Appendix D for completeness. The ELIANA trial is the pivotal trial that informed the marketing authorisation for tisagenlecleucel in this indication, has the longest follow-up and is most generalisable to the intended patient population and use of tisagenlecleucel in UK clinical practice, as noted by the committee in TA554.[9] The comparison of the matched and unmatched tisagenlecleucel curves found little difference in efficacy estimates, with overlapping 95% confidence intervals indicating that differences between the matched and unmatched curves may reflect uncertainty inherent in the sample estimates rather than a true difference in efficacy, supporting the use of naïve comparisons informing the economic model.

The limited maturity of clinical data to inform the long-term survival extrapolation of tisagenlecleucel, particularly in the use of mixture-cure models, was raised as a concern by the ERG in the original appraisal (TA554). Whilst the availability of long-term data from the ELIANA trial mitigates the uncertainty for the tisagenlecleucel survival extrapolations, comparator efficacy data sources remain limited in their data maturity. To model the treatment of r/r B-cell ALL patient population of interest as accurately as possible, base case survival extrapolations were extensively validated with clinical experts as part of this submission. However, given tisagenlecleucel (reimbursed via the CDF) is already established as a treatment option in clinical practice, recent clinical experience of comparator therapies, and thus the resulting clinical expectations around predicted survival and cost inputs, may be biased, reflecting a world with tisagenlecleucel, rather than a world without tisagenlecleucel.

Although there were no UK centres in the tisagenlecleucel clinical trials, the patient population enrolled in the pivotal ELIANA clinical trial included some EU5 countries (France, Germany, Italy and Spain) and can be considered generalisable to the relevant patient population in the UK, based on UK clinical expert feedback gathered as part of the original appraisal (TA554).[4] This analysis provides the most robust comparison of relative efficacy of tisagenlecleucel with UK clinical management of r/r B-cell ALL in paediatric and young adult patients.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 Summary of base case analysis inputs

A summary of the key base case analysis inputs is presented in Table 65.

Table 65: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs)	3.50%	Section B.3.2.2
Discount rate (benefits)	3.50%	
Time horizon	88 years	
Patient characteristics		
Starting age (years)	12	Section B.3.3.1
Percent female	43.04%	
Mean BSA	1.25 m^2	
Mean weight (kg)	41.52 kg	
Efficacy		
OS distribution (tisagenlecleucel)	Log-logistic	Section B.3.3.3
EFS distribution (tisagenlecleucel)	Log-logistic	
OS distribution (salvage chemotherapy [FLAG-IDA])	Log-normal	
EFS distribution (salvage chemotherapy [FLAG-IDA])	Based on OS	
OS distribution (blinatumomab)	Log-normal	
EFS distribution (blinatumomab)	Based on OS	
Subsequent allo-SCT		
Subsequent allo-SCT rate for tisagenlecleucel	22.78%	Section B.3.5.1
Subsequent allo-SCT rate for salvage chemotherapy (FLAG-IDA)	14.75%	
Subsequent allo-SCT rate for blinatumomab	34.29%	
Allo-SCT disutility (per month)	-0.048	Section B.3.4.5
Allo-SCT cost	£151,277.43	Section B.3.5.1
Health state utilities and disutilities		
Utility for EFS	0.91	Section B.3.4.5
Utility for PD	0.75	
Disutility for tisagenlecleucel[a]	-0.03	Section B.3.4.4
Disutility for salvage chemotherapy[a]	-0.02	
Disutility for blinatumomab[a]	-0.01	
Health state costs		
Follow-up medical costs per cycle in EFS for tisagenlecleucel	Year 1:[b] £472.58 Year 2: £111.87 Year 3-5: £56.18 Year 5+: £27.47	Section B.3.5.2
Follow-up medical costs per cycle in EFS for comparators	Year 1: £263.00 Year 2: £110.86 Year 3-5: £55.43	

	Year 5+: £27.47	
Medical costs per cycle in PD (year 1) for tisagenlecleucel[b]	£191.00	
Medical costs per cycle in PD (year 1) and PD (year 1 and post 1 year) for comparators (blinatumomab and salvage chemotherapy)	£263.00	
One-time terminal care cost	£13,198.42	
Drug acquisition and administration (with NHS CAR-T tariff)[c]		
NHS CAR-T Tariff (tisagenlecleucel, base case)[c]	£41,101.00	Section B.3.5.1
Pre-treatment costs (tisagenlecleucel)		
Leukapheresis[c]	£2,575.70	
Bridging chemotherapy[d]	£1,394.57	
Lymphodepleting chemotherapy[d]	£404.52	
Treatment costs		
Procedure/treatment	Tisagenlecleucel: £282,000.00 Salvage chemotherapy: £1,413.82 Blinatumomab: £71,805.20	Section B.3.5.1
Administration cost	Tisagenlecleucel:[c] £24,921.47	
Outpatient administration cost	Blinatumomab: £8,720.16	
Hospitalisation cost	Tisagenlecleucel:[c] £8,867.00 Salvage chemotherapy: £20,245.68 Blinatumomab: £8,910.86	
Cost of AEs (with NHS CAR-T tariff)[c]		
AEs	Tisagenlecleucel:[c] £11,176.85 Salvage chemotherapy: £1,802.56 Blinatumomab: £2,847.49	Section B.3.5.3

[a]Treatment disutility values were dependent on disutility duration whereby the disutility duration for salvage chemotherapy was assumed to be the same as the length of induction and consolidation regimens. The disutility duration for tisagenlecleucel was assumed to be the same as the length of hospital stay after infusion. All treatments had a fixed monthly disutility value of -0.42.
[b]Costs calculated after applying NHS tariff which covers follow-up costs for the first 100 days after infusion.
[c]The NHS CAR-T tariff has been considered in the base case analysis whereby the CAR T-cell administration cost of £41,101 covers leukapheresis, CAR T-cell administration, AEs, monitoring, training. The costs for bridging chemotherapy drugs and its administration, SCT and IVIg are applied separately. The NHS tariff covering the cost of tisagenlecleucel administration was sourced from the NICE appraisal for brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893).[58]
[d]Not included in NHS CAR-T tariff; included in all analyses.
Abbreviations: AIC: Akaike information criterion; AE: adverse event; BSA: body surface area; CI: confidence interval; EFS: event-free survival; NA: not applicable; OS: overall survival; PD: progressed disease; PFS: progression-free survival; SE: standard error.

B.3.8.2 Assumptions

A list of the assumptions used in the base case analysis is provided in Table 66 alongside a list of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results. The results of these scenario analyses are presented in Section B.3.10.3.

Table 66: List of assumptions for the base case analysis

Parameter	Assumption	Justification	Addressed in scenario analyses
Health states and utilities by health states	• Health state utility values are independent of treatment received	• In the absence of health state utility values by individual treatment in the pALL indication, no differences in health state utility values by treatment were assumed • This assumption was employed in the original submission (TA554) and accepted by the committee	• N/A
Where EFS data are unavailable, EFS can be assumed to have a proportional hazards relationship to OS	• EFS data were not reported for salvage chemotherapy or blinatumomab • Therefore, in the base case EFS for these comparators was estimated based on the OS data assuming a constant cumulative HR over time • The ratio between EFS and OS was modelled based on data from the UK ALL study, a study of mitoxantrone in children with a first relapse of ALL.[54]	• This approach was employed in the original submission (TA554) and accepted by the ERG[9] • Clinicians consulted as part of this submission also indicated that the EFS and OS curves should be closely matched[4]	• N/A
Patients in the tisagenlecleucel arm who do not receive tisagenlecleucel infusion are assumed	• A proportion of patients in the clinical trials of tisagenlecleucel did not go on to receive tisagenlecleucel due to manufacture failure or withdrawal due to adverse events or death in	• This was considered a realistic representation of what would happen in clinical practice, confirmed by expert UK clinician feedback consulted as part of this submission[4]	• N/A

Parameter	Assumption	Justification	Addressed in scenario analyses
to receive comparator therapies	the period post-leukapheresis and pre-infusion • It was assumed that the surviving patients would therefore instead receive the comparator therapies and be associated with the total cost and total QALYs for the comparator arms. A equal weighting of salvage chemotherapy and blinatumomab outcomes was assumed		
Patients who do not receive tisagenlecleucel infusion accrue the costs associated with leukapheresis, cryopreservation and bridging chemotherapy but do not accrue QALYs for the pre-infusion period	• Health state utility values are independent of treatment received	• In the absence of health state utility values by individual treatment in the pALL indication, no differences in health state utility values by treatment were assumed • Extrapolatory analyses performed by the ERG in the original appraisal (TA554) suggested that the impact of this assumption is minimal and therefore, has not been explored further in this submission[9]	• N/A
SMR for long-term ALL survival	• The overall survival profile for all treatments was bounded by general population mortality adjusted by a SMR of 4	• Adjustment of general population mortality for ALL survivors was required to ensure no logical inconsistencies were introduced due to the use of mixture cure models (where cured patients are assumed to follow general population mortality), whereby surviving patients experienced lower mortality rates than would be expected for long-term ALL survivors • There was consensus among clinical	• A scenario analysis in which a SMR of 9.05 derived from MacArthur et al. (2007) was used to bound general population mortality; this is expected to be a conservative estimate based on feedback from clinical experts[4, 119]

Parameter	Assumption	Justification	Addressed in scenario analyses
		experts that general population mortality adjusted by a SMR of 4 was most appropriate, in line with the expectation that long-term survivors following treatment would experience an increased mortality risk compared with the general population[4]	
Length of ICU hospitalisation	• The length of ICU stay following treatment with tisagenlecleucel is based on ELIANA trial data	• The ELIANA trial reported length of ICU stay due to CRS and length of ICU stay for reasons other than ICU. As the principal source of evidence for tisagenlecleucel in this submission, these data were chosen to inform the base case analysis	• Clinical expert feedback noted that length of ICU stay due to CRS may be shorter in NHS clinical practice[4] • A scenario analysis assuming an average ICU stay of 3 days was explored, based on clinical feedback[4] • As no data were available to inform length of ICU stay for reasons other than CRS, this value was derived from total and CRS-related ICU stay data from ELIANA. In order to avoid a large increase in ICU stay for reasons other than CRS, length of ICU stay due to reasons other than CRS was adjusted proportionally
Proportion of patients receiving IVIg treatment	• In the base case economic analysis, 75% of patients experiencing hypogammaglobulinaemia following treatment with tisagenlecleucel are assumed to receive treatment with IVIg	• Clinical feedback received as part of this appraisal noted that not all patients experiencing hypogammaglobulinaemia receive IVIg in NHS practice[4] • The lower proportion of patients receiving IVIg for hypogammaglobulinaemia is in line with ERG feedback as part of TA554, which indicated that the company estimate of patients receiving IVIg	• A scenario was explored in which all patients experiencing hypogammaglobulinaemia are assumed to receive IVIg treatment

Parameter	Assumption	Justification	Addressed in scenario analyses
		was likely too high[9]	
Proportion of patients receiving allo-SCT	• The proportion of patients receiving allo-SCT is based on the respective treatment efficacy sources	• Given the introduction of tisagenlecleucel in this indication via the CDF, and its establishment as the primary treatment option, treatment with comparators is now likely to be tailored in patients with greater likelihood of successfully bridging to allo-SCT and therefore may not reflect the full population eligible for tisagenlecleucel • As detailed in Section B.3.3.2, this is likely to have biased clinician estimates towards higher rates of allo-SCT than would be observed were tisagenlecleucel not available • Given the uncertainty in these estimates, and in order to ensure fair comparisons between tisagenlecleucel and comparators, rates of subsequent allo-SCT were obtained from the clinical sources used for the efficacy inputs, rather than from clinician estimates • These may better reflect clinical practice prior to the introduction of tisagenlecleucel as well as the expected subsequent allo-SCT rates for comparators when considered in the full population eligible for tisagenlecleucel in clinical practice	• A scenario analysis is explored in using real-world data for tisagenlecleucel during the managed access period, showing 12.28% of patients received a subsequent SCT.[3]

Abbreviations: AE: adverse event; ALL: acute lymphoblastic leukaemia; allo-SCT: haematopoietic stem cell transplantation; CDF: Cancer Drugs Fund; CRS: cytokine-release syndrome; EFS: event-free survival; IVIg: intravenous immunoglobin; OS: overall survival; SMR: standardised mortality ratio.

B.3.9 *Base-case results*

B.3.9.1 Base case cost-effectiveness analysis results

A summary of the deterministic base case economic analysis results is presented in Table 68 (with tisagenlecleucel at list price) and Table 69 (with tisagenlecleucel at PAS price). Clinical feedback suggested that blinatumomab is the preferred treatment option in clinical practice, with salvage chemotherapy rarely used. As such, a fully incremental analysis was not conducted.

At list price, tisagenlecleucel is associated with [redacted] and [redacted] more QALYs at an incremental cost of [redacted] and [redacted] versus blinatumomab and salvage chemotherapy respectively. The resulting list price ICERs versus blinatumomab and salvage chemotherapy are [redacted] and [redacted] per QALY gained.

As discussed in Section B.3.6 above, r/r B-cell ALL is a severe disease, and satisfies the criteria for a severity modifier of 1.7. When the severity modifier is applied, the resulting list (and PAS) price ICERs versus blinatumomab and salvage chemotherapy are [redacted] (£11,304) and [redacted] (£18,105) per QALY gained: both below the lower bound of the threshold range used to define cost-effectiveness.

As discussed in Section B.3.2.2, Novartis also believe that NICE's criteria for a non-reference case discount rate of 1.5% are met. The cumulative impact of application of the 1.7 severity modifier and 1.5% discount rate is a reduction of base case list price ICERs versus blinatumomab and salvage chemotherapy to [redacted] and [redacted] respectively. These ICERs are further reduced to £7,708 and £12,462 vs. the respective comparators when the PAS for tisagenlecleucel is applied. In conclusion tisagenlecleucel represents a highly cost-effective and potentially curative intervention for this population of mostly young children.

A summary of deterministic base case ICERs under different settings is provided in Table 67. A summary of the disaggregated costs and QALYs per health state is presented in Appendix J.

Table 67: Summary of base case ICERs under different model settings

Model setting	ICER incr. £/QALY	
	versus blinatumomab	versus salvage chemotherapy
Base Case at Tisagenlecleucel List Price	[redacted]	[redacted]
Base Case at Tisagenlecleucel PAS Price	19,218	30,778
Base Case at Tisagenlecleucel List Price and 1.7 Severity Modifier	[redacted]	[redacted]
Base Case at Tisagenlecleucel PAS Price and 1.7 Severity Modifier	11,304	18,105
Base case at Tisagenlecleucel List Price and 1.7 Severity Modifier and 1.5% Discount rate	[redacted]	[redacted]
Base Case at Tisagenlecleucel PAS Price and 1.7 Severity Modifier and 1.5% Discount rate	7,708	12,462

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 68: Deterministic base case results (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	NHB at £20K	NHB at £30K
Tisagenlecleucel	[redacted]	10.84	[redacted]	-					
Blinatumomab	158,289	3.71	3.06	[redacted]	7.13	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	59,980	2.66	2.22	[redacted]	8.18	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 69: Deterministic base case results (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	NHB at £20K	NHB at £30K
Tisagenlecleucel	[redacted]	10.84	[redacted]	-					
Blinatumomab	158,289	3.71	3.06	[redacted]	7.13	[redacted]	19,218	[redacted]	[redacted]
Salvage chemotherapy	59,980	2.66	2.22	[redacted]	8.18	[redacted]	30,778	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 70: Deterministic base case results (tisagenlecleucel list price; x1.7 severity modifier applied)

Intervention	Incr. QALYs	ICER incr. £/QALY	NHB at £20K	NHB at £30K
Tisagenlecleucel	-			
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 71: Deterministic base case results (tisagenlecleucel PAS price; x1.7 severity modifier applied)

Intervention	Incr. QALYs	ICER incr. £/QALY	NHB at £20K	NHB at £30K
Tisagenlecleucel	-			
Blinatumomab	[redacted]	11,304	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	18,105	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

B.3.10 *Exploring uncertainty*

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted using a Monte-Carlo simulation with 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specified distributions summarised in Appendix J. The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original IPD or pseudo-IPD data used for the OS and (where available) EFS estimation in the base case. For each PSA iteration, the base case parametric function parameters for each arm were estimated based on one bootstrapped sample.

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost parameter was assumed to be equal to the mean value divided by four. For the utility values, it was assumed that the utility of the progressed/relapsed disease health state should not exceed the utility of the EFS health state, with the ordering preserved using the difference method for sampling ordered parameters (Ren *et al.* [2018]).[158]

A complete list of the PSA inputs is presented in in Appendix K and the results of the PSA (1,000 iterations) are presented from Table 72 to Table 75 for tisagenlecleucel at list price, PAS price, list price with x1.7 severity modifier applied and PAS price with x1.7 severity modifier applied, respectively. The probabilistic results (that take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis, confirming the robustness of the base case analysis at both list and PAS prices.

Table 72: Probabilistic results (tisagenlecleucel list price)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Blinatumomab	159,068	3.88	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	60,538	2.62	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 73: Probabilistic results (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Blinatumomab	158,926	3.81	[redacted]	[redacted]	19,449
Salvage chemotherapy	59,999	2.62	[redacted]	[redacted]	29,759

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 74: Probabilistic results (tisagenlecleucel list price; x1.7 severity modifier)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Blinatumomab	157,349	3.79	[redacted]	[redacted]	[redacted]

Salvage chemotherapy	59,995	2.82	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 75: Probabilistic results (tisagenlecleucel PAS price; x1.7 severity modifier)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Blinatumomab	159,497	3.85	[redacted]	[redacted]	11,655
Salvage chemotherapy	60,400	2.64	[redacted]	[redacted]	17,669

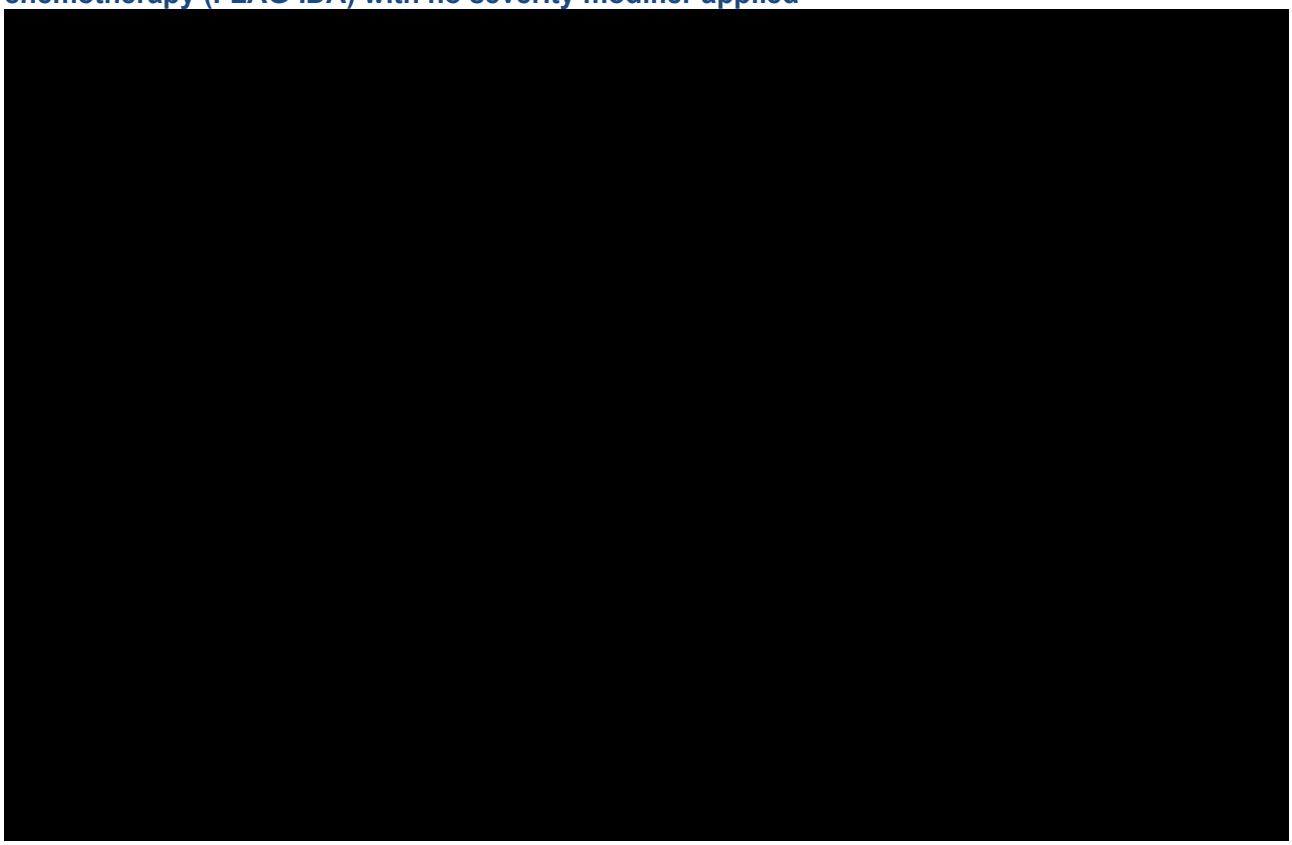
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Scatter plots showing the incremental costs and QALYs for tisagenlecleucel (list price) with no severity modifier applied versus blinatumomab and salvage chemotherapy (FLAG-IDA) are presented in Figure 37 and Figure 38, respectively.

Figure 37: Cost-effectiveness plane: tisagenlecleucel (list price) versus blinatumomab with no severity modifier applied

Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 38: Cost-effectiveness plane: tisagenlecleucel (list price) versus salvage chemotherapy (FLAG-IDA) with no severity modifier applied



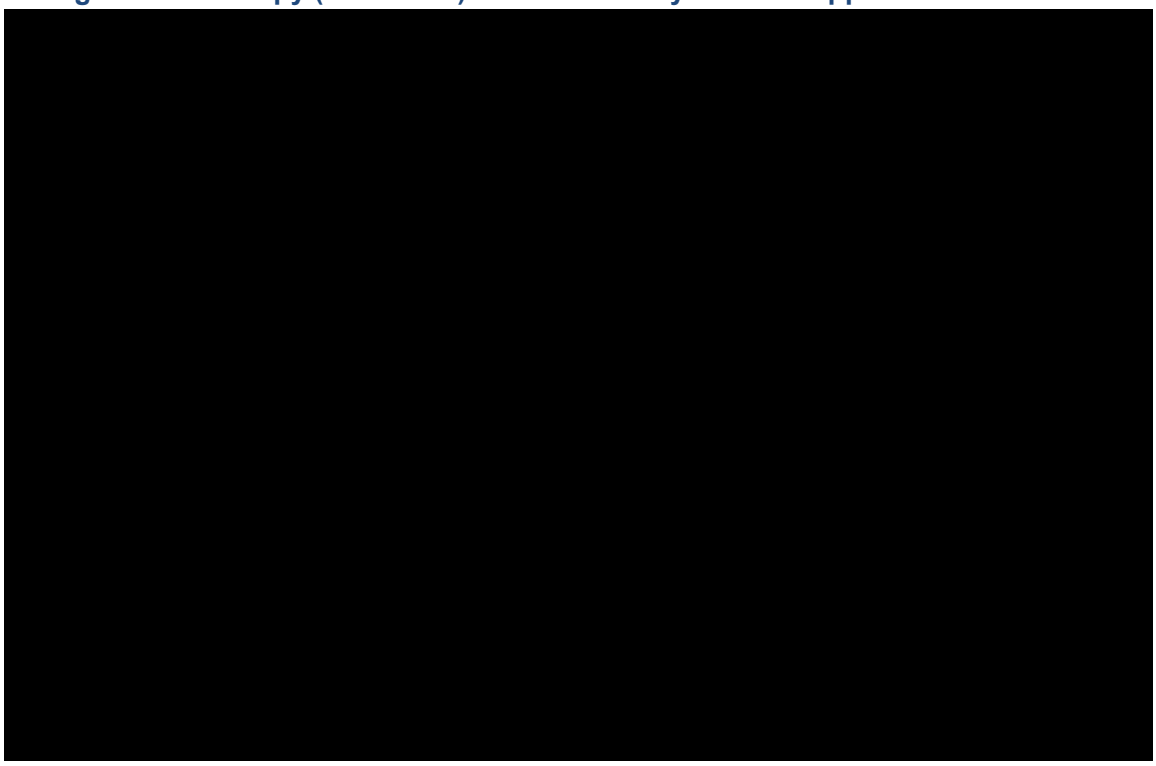
Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Cost-effectiveness acceptability curves for tisagenlecleucel (list price) with no severity modifier applied versus blinatumomab and salvage chemotherapy (FLAG-IDA) are presented in Figure 39 and Figure 40, respectively. When considering tisagenlecleucel at list price and a cost-effectiveness threshold of £30,000 per QALY with no severity modifier applied, the probability of tisagenlecleucel being cost-effective compared to blinatumomab and salvage chemotherapy (FLAG-IDA) is [redacted] and [redacted] respectively.

Figure 39: Cost-effectiveness acceptability curve: tisagenlecleucel (list price) versus blinatumomab with no severity modifier applied

*Note CTL019 = tisagenlecleucel
Abbreviations: WTP: willing-ness to pay.

Figure 40: Cost-effectiveness acceptability curve: tisagenlecleucel (list price) versus salvage chemotherapy (FLAG-IDA) with no severity modifier applied



*Note CTL019 = tisagenlecleucel
Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; WTP: willing-ness to pay.

Scatter plots showing the incremental costs and QALYs for tisagenlecleucel (PAS price) with the x1.7 severity modifier applied versus blinatumomab and salvage chemotherapy (FLAG-IDA) are presented in Figure 41 and Figure 42, respectively.

Figure 41: Cost-effectiveness plane: tisagenlecleucel (PAS price) versus blinatumomab with x1.7 severity modifier applied

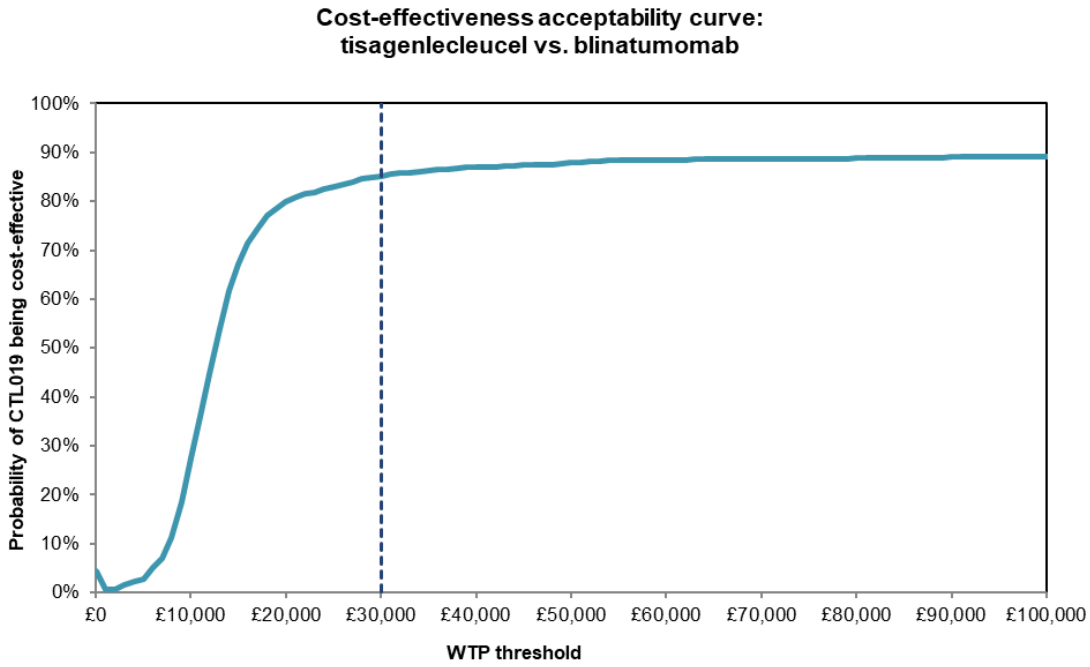
Abbreviations: PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 42: Cost-effectiveness plane: tisagenlecleucel (PAS price) versus salvage chemotherapy (FLAG-IDA) with x1.7 severity modifier applied

Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

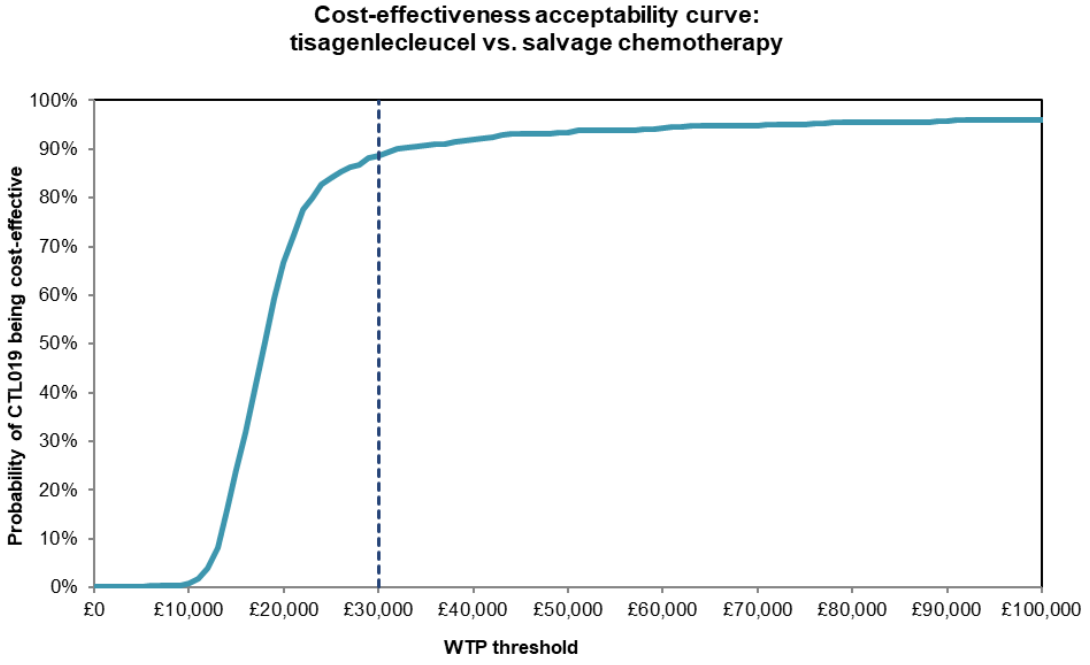
Cost-effectiveness acceptability curves for tisagenlecleucel (PAS price) with the x1.7 severity modifier applied versus blinatumomab and salvage chemotherapy (FLAG-IDA) are presented in Figure 39 and Figure 40, respectively. When considering tisagenlecleucel at PAS price and a cost-effectiveness threshold of £30,000 per QALY with a x1.7 severity modifier applied, the probability of tisagenlecleucel being cost-effective compared to blinatumomab and salvage chemotherapy (FLAG-IDA) is [redacted] and [redacted] respectively.

Figure 43: Cost-effectiveness acceptability curve: tisagenlecleucel (PAS price) versus blinatumomab with x1.7 severity modifier applied



*Note CTL019 = tisagenlecleucel
Abbreviations: WTP: willing-ness to pay.

Figure 44: Cost-effectiveness acceptability curve: tisagenlecleucel (PAS price) versus salvage chemotherapy (FLAG-IDA) with x1.7 severity modifier applied



*Note CTL019 = tisagenlecleucel
Abbreviations: FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; PAS: patient access scheme; WTP: willing-ness to pay.

B.3.10.2 Deterministic sensitivity analysis

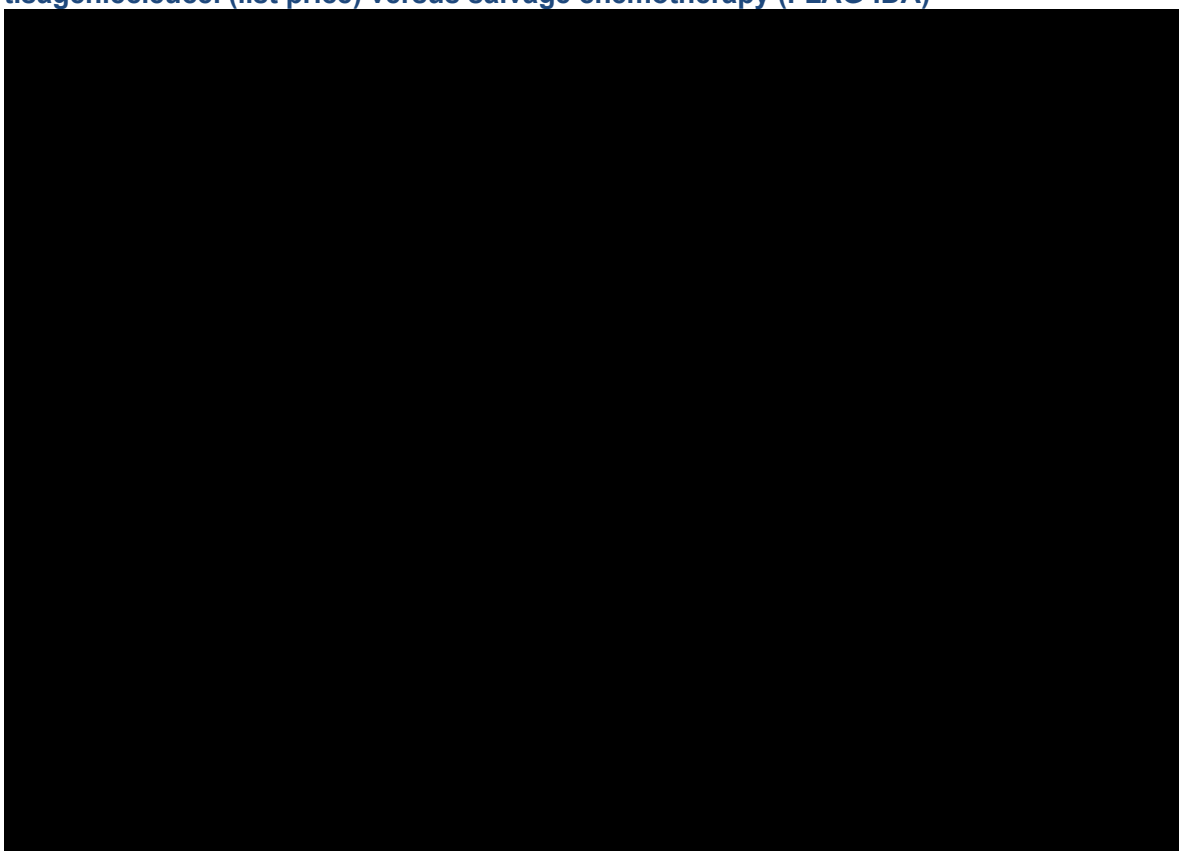
Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values in the model by the upper and lower bounds of the 95% CI, or by ±25% of their mean value (where 95% Cis were not available). The DSA inputs are presented in Appendix K. Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of tisagenlecleucel versus blinatumomab and salvage chemotherapy (FLAG-IDA) are presented in Figure 45 and Figure 46, respectively, when tisagenlecleucel is provided at list price.

Across the tornado diagrams it can be seen that versus both comparators, the subsequent allo-SCT rate and utility values for EFS were key drivers of the economic model, consistent with what was observed in the original appraisal (TA554).[9] For blinatumomab, the treatment cost was also key in driving the model outputs.

Figure 45: Tornado diagram of the ten most influential parameters from the DSA: tisagenlecleucel (list price) versus blinatumomab

Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; EFS: event-free survival; PD: relapsed/progressed disease; SCT: stem cell transplant.

Figure 46: Tornado diagram of the ten most influential parameters from the DSA: tisagenlecleucel (list price) versus salvage chemotherapy (FLAG-IDA)



Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; EFS: event-free survival; FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; G-CSF: granulocyte-colony stimulating factor; SCT: stem cell transplant.

B.3.10.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis, and are outlined in Table 76 below. The probabilistic scenario results of these scenarios are presented in Table 77 and Table 78 for tisagenlecleucel at list price, without and with the x1.7 severity modifier respectively. The probabilistic scenario results for tisagenlecleucel at PAS price, without and with the x1.7 severity modifier applied are presented in

Table 79 and Table 80 respectively. Across all of the scenarios conducted, it can be demonstrated that changes made to the modelling approach and assumptions do not result in material changes to the ICERs. The largest change in ICER can be observed in the time horizon ICERs (the ICERs increase as the time horizon decreases), though this is to be expected given the large upfront costs for tisagenlecleucel.

Table 76: Scenario analyses explored in the economic analysis

#	Scenario analysis	Rationale
Efficacy based on alternative parametric mixture cure models		
1	Tisagenlecleucel OS: Log-normal	In the base case, a log-logistic mixture cure extrapolation was selected as this curve generated the most plausible long-term survival outcomes, based on input from clinical experts. Log-normal and Gompertz models produced clinically plausible results, and were explored as more pessimistic and optimistic extrapolations, respectively. Extrapolations of EFS data from ELIANA were all very similar, with little difference in predicted long term outcomes, and as such no scenario analyses were conducted for EFS. The similarity in these extrapolations demonstrates the robust nature of the long-term ELIANA data informing survival in the model.
2	Tisagenlecleucel OS: Gompertz	
3	Blinatumomab OS: Log-logistic	In the base case, a log-normal was used in the base case analysis, as this most closely reflected long-term survival estimates provided by clinicians, when considering survival outcomes expected in a world *without* tisagenlecleucel. The log-logistic provided the only other plausible estimate of survival for blinatumomab, and was additionally explored as a scenario analysis.
Utility		
4	Utility Source: ELIANA trial	Given the limited sample size of EQ-5D available from the ELIANA trial, it was considered more appropriate to use the values from Kelly *et al.* (2015) in the base case, as was accepted by committee in the original submission. However, the study is associated with limitations (see Section B.3.4.3), and no additional relevant studies were identified in the SLR. The use of ELIANA EQ-5D data to inform utility estimates was therefore explored as a scenario analysis. Additionally, in line with ERG preference in TA554, a scenario analysis was explored in which ELIANA data informed utility estimates for the first two years of the model, followed by Kelly *et al.* (2015).
5	ELIANA utility for first two years (no treatment or AE disutilities applied)	
6	Disutility associated with SCT derived from Sung *et al.* (-0.57) for three months followed by Felder-Puig *et al.* (-0.13) for nine months	The ERG noted in the original appraisal (TA554) that the utility decrements estimated by Sung *et al.* (2003) may overestimate the duration of the persistence of the utility decrement following allo-SCT. The base case approach, where disutility was assumed to last for one year post treatment initiation, was consistent with the NICE mock appraisal,[137] and the ERG's preference was explored as a conservative scenario.
Costs		
7	All patients experiencing hypogammaglobulinaemia assumed to receive IVIg	Clinical opinion to the ERG in the original submission was that only patients with hypogammaglobulinaemia would receive IVIg. Clinical expert opinion indicated that not all patients with hypogammaglobulinaemia would receive IVIg treatment, but

		approximately 75% of patients would, which is the approach taken in the base case analysis. A conservative scenario analysis was explored in which all patients with hypogammaglobulinaemia are assumed to receive treatment with IVIg.
8	Patients receiving blinatumomab assumed to receive IVIg	The source informing the efficacy inputs for blinatumomab, von Stackelberg *et al.* (2016), did not report data relating to the incidence of hypogammaglobulinaemia, and was therefore not included in the base case analysis. However, this is a commonly reported AE in adult patients, and its inclusion as an AE in the paediatric population has been explored as a scenario analysis. Incidence for hypogammaglobulinaemia has been sourced from the phase III TOWER trial investigating blinatumomab versus chemotherapy in adult patients with ALL.[57] Median duration of IVIg treatment was assumed equal to tisagenlecleucel, as reported in the 22nd November 2022 DCO of the ELIANA trial.
9	Duration of CRS-related ICU admission based on clinician estimates	In the base case analysis, the length of ICU stay is based on ICU admission data reported in the ELIANA trial. However, clinical expert feedback noted that length of ICU stay due to CRS may be shorter in NHS clinical practice. A scenario analysis assuming an average ICU stay of 3 days was explored, based on clinical feedback. Length of ICU stay due to reasons other than CRS was adjusted proportionally in this scenario.
10	Vial sharing assumed	In the base case, no vial sharing is assumed. However, as some treatments included in the model may allow for vial sharing to be implemented in practice, a scenario has been conducted to assess the impact of this on the cost-effectiveness results
11	Resource use source: NHS reference costs	In the latest appraisal for a CAR-T therapy in ALL, TA893, the committee's preference was for the cost of leukapheresis, treatment administration, management of adverse events, monitoring and training required for treatment with tisagenlecleucel to be accounted for via a tariff of £41,101 established by the NHS for the use of CAR-T therapies. To align with committee preference, this approach was taken in the base case analysis in this submission. However, this remains an estimation of different costs, projected onto a single treatment. In order to explore uncertainty associated with this estimate, a scenario analysis was conducted in which the costs covered by the NHS tariff are costed individually.
12	Tocilizumab discount assumed to be 20%	In the absence of knowledge of the PAS discount for tocilizumab (used to treat CRS), a 20% discount was explored as a scenario analysis.
Long-term assumptions		
13	SMR adjustment to general population mortality: 9.05	All mortality rates used in the model were bound by SMR-adjusted age- and gender-specific natural mortality of the general population as a minimum. In the base case analysis, a SMR value was used, in line with clinical feedback received as part of this appraisal. As a conservative estimate, and in line with the previous approach used in the original submission, a SMR value of 9.05 was used in a scenario analysis, based on MacArthur *et al.* (2007).[119]
Additional scenarios		

14	Discount rate of 1.5% applied	The NICE reference case stipulates that a non-reference case discount rate of 1.5% may be applied if the following criteria are met: • The technology is for people who would otherwise die or have a very severely impaired life. • It is likely to restore them to full or near-full health. • The benefits are likely to be sustained over a very long period. Given the extremely poor prognosis facing patients in this population, and proven long-term curative potential of tisagenlecleucel, Novartis believe that these conditions are clearly met, and have therefore explored a scenario analysis in which a 1.5% discount is applied to both costs and health outcomes.
15	Subsequent SCT rate for tisagenlecleucel: NDRS report	Real-world use of tisagenlecleucel during the managed access period, based on the NHSE CDF report confirmed that 12.28% of patients received a subsequent SCT.[3] This is explored as a scenario.

Abbreviations: AE: adverse event; ALL: acute lymphoblastic leukaemia; CAR-T: chimeric antigen receptor-T cell; CDF: Cancer Drugs Fund; CRS: cytokine release syndrome; DCO: data cut-off; EFS: event-free survival; EQ-5D: European quality of life 5-Dimensions; ERG: Evidence Review Group; NDRS: National Disease Registration Services; NICE: National Institute for Health and Care Excellence; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobin; NHS: National Health Service; NHSE: National Health Service England; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years; SCT: stem cell transplant; SLR: systematic literature review; SMR: standardised mortality ratio; TA: technology appraisal.

Table 77: Scenario analyses probabilistic results (tisagenlecleucel list price; no severity modifier applied)

#	Scenario	Versus blinatumomab			Versus salvage chemotherapy		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy based on alternative parametric functions for all treatment arms							
1	Tisagenlecleucel OS: Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Tisagenlecleucel OS: Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Blinatumomab OS: Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility							
4	Utility Source: ELIANA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	ELIANA utility for first two years (no treatment or AE disutilities applied)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Disutility associated with SCT derived from Sung et al. (-0.57) for three months followed by Felder-Puig et al. (-0.13) for nine months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs							
7	All patients experiencing hypogammaglobulinaemia assumed to receive IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Patients receiving blinatumomab assumed to receive IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Duration of CRS-related ICU admission based on clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Vial sharing assumed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Resource use source: NHS reference costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12	Tocilizumab discount assumed to be 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term assumptions							
13	SMR adjustment to general population mortality: 9.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional scenarios							
14	Discount rate of 1.5% applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	Subsequent SCT rate for tisagenlecleucel: NDRS report	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobin; NDRS: National Disease Registration Services; NHS: National Health Service; OS: overall survival; QALYs: quality-adjusted life years; SCT: stem cell transplant; SMR: standardised mortality ratio.

Table 78: Scenario analyses probabilistic results (tisagenlecleucel PAS price; no severity modifier applied)

#	Scenario	Versus blinatumomab			Versus salvage chemotherapy		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	19,449	[redacted]	[redacted]	29,759
Efficacy based on alternative parametric functions for all treatment arms							
1	Tisagenlecleucel OS: Log-normal	[redacted]	[redacted]	19,476	[redacted]	[redacted]	29,104
2	Tisagenlecleucel OS: Gompertz	[redacted]	[redacted]	13,694	[redacted]	[redacted]	21,641
3	Blinatumomab OS: Log-logistic	[redacted]	[redacted]	20,324	[redacted]	[redacted]	30,032
Utility							
4	Utility Source: ELIANA trial	[redacted]	[redacted]	22,247	[redacted]	[redacted]	33,448
5	ELIANA utility for first two years (no treatment or AE disutilities applied)	[redacted]	[redacted]	21,943	[redacted]	[redacted]	33,153
6	Disutility associated with SCT derived from Sung et al. (-0.57) for three months followed by Felder-Puig et al. (-0.13) for nine months	[redacted]	[redacted]	19,757	[redacted]	[redacted]	29,877

Costs							
7	All patients experiencing hypogammaglobulinaemia assumed to receive IVIg	[redacted]	[redacted]	20,503	[redacted]	[redacted]	30,382
8	Patients receiving blinatumomab assumed to receive IVIg	[redacted]	[redacted]	19,659	[redacted]	[redacted]	30,152
9	Duration of CRS-related ICU admission based on clinician estimates	[redacted]	[redacted]	19,981	[redacted]	[redacted]	29,673
10	Vial sharing assumed	[redacted]	[redacted]	26,227	[redacted]	[redacted]	29,786
11	Resource use source: NHS reference costs	[redacted]	[redacted]	21,564	[redacted]	[redacted]	31,606
12	Tocilizumab discount assumed to be 20%	[redacted]	[redacted]	19,689	[redacted]	[redacted]	29,669
Long-term assumptions							
13	SMR adjustment to general population mortality: 9.05	[redacted]	[redacted]	20,933	[redacted]	[redacted]	30,581
Additional scenarios							
14	Discount rate of 1.5% applied	[redacted]	[redacted]	13,365	[redacted]	[redacted]	20,444
15	Subsequent SCT rate for tisagenlecleucel: NDRS report	[redacted]	[redacted]	18,191	[redacted]	[redacted]	28,645

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobin; NDRS: National Disease Registration Services; NHS: National Health Service; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years; SCT: stem cell transplant; SMR: standardised mortality ratio.

Table 79: Scenario analyses probabilistic results (tisagenlecleucel list price; x1.7 severity modifier applied)

#	Scenario	Versus blinatumomab			Versus salvage chemotherapy		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy based on alternative parametric functions for all treatment arms							
1	Tisagenlecleucel OS: Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Tisagenlecleucel OS: Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Blinatumomab OS: Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility							
4	Utility Source: ELIANA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	ELIANA utility for first two years (no treatment or AE disutilities applied)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Disutility associated with SCT derived from Sung et al. (-0.57) for three months followed by Felder-Puig et al. (-0.13) for nine months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs							
7	All patients experiencing hypogammaglobulinaemia assumed to receive IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Patients receiving blinatumomab assumed to receive IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Duration of CRS-related ICU admission based on clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Vial sharing assumed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Resource use source: NHS reference costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12	Tocilizumab discount assumed to be 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term assumptions							
13	SMR adjustment to general population mortality: 9.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional scenarios							
14	Discount rate of 1.5% applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	Subsequent SCT rate for tisagenlecleucel: NDRS report	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobin; NDRS: National Disease Registration Services; NHS: National Health Service; OS: overall survival; QALYs: quality-adjusted life years; SCT: stem cell transplant; SMR: standardised mortality ratio.

Table 80: Scenario analyses probabilistic results (tisagenlecleucel PAS price; x1.7 severity modifier applied)

#	Scenario	Versus blinatumomab			Versus salvage chemotherapy		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	11,655	[redacted]	[redacted]	17,669
Efficacy based on alternative parametric functions for all treatment arms							
1	Tisagenlecleucel OS: Log-normal	[redacted]	[redacted]	11,520	[redacted]	[redacted]	17,325
2	Tisagenlecleucel OS: Gompertz	[redacted]	[redacted]	8,399	[redacted]	[redacted]	12,772
3	Blinatumomab OS: Log-logistic	[redacted]	[redacted]	12,299	[redacted]	[redacted]	17,627
Utility							
4	Utility Source: ELIANA trial	[redacted]	[redacted]	13,053	[redacted]	[redacted]	19,496
5	ELIANA utility for first two years (no treatment or AE disutilities applied)	[redacted]	[redacted]	13,104	[redacted]	[redacted]	19,474
6	Disutility associated with SCT derived from Sung et al. (-0.57) for	[redacted]	[redacted]	11,796	[redacted]	[redacted]	17,591

	three months followed by Felder-Puig et al. (-0.13) for nine months						
Costs							
7	All patients experiencing hypogammaglobulinaemia assumed to receive IVIg	[redacted]	[redacted]	12,213	[redacted]	[redacted]	17,794
8	Patients receiving blinatumomab assumed to receive IVIg	[redacted]	[redacted]	11,817	[redacted]	[redacted]	17,899
9	Duration of CRS-related ICU admission based on clinician estimates	[redacted]	[redacted]	12,132	[redacted]	[redacted]	17,702
10	Vial sharing assumed	[redacted]	[redacted]	15,669	[redacted]	[redacted]	17,390
11	Resource use source: NHS reference costs	[redacted]	[redacted]	12,944	[redacted]	[redacted]	18,470
12	Tocilizumab discount assumed to be 20%	[redacted]	[redacted]	12,119	[redacted]	[redacted]	17,696
Long-term assumptions							
13	SMR adjustment to general population mortality: 9.05	[redacted]	[redacted]	12,363	[redacted]	[redacted]	18,088
Additional scenarios							
14	Discount rate of 1.5% applied	[redacted]	[redacted]	7,922	[redacted]	[redacted]	12,108
15	Subsequent SCT rate for tisagenlecleucel: NDRS report	[redacted]	[redacted]	10,910	[redacted]	[redacted]	17,006

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobin; NDRS: National Disease Registration Services; NHS: National Health Service; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years; SCT: stem cell transplant; SMR: standardised mortality ratio.

B.3.11 *Subgroup analysis*

Given the paucity of data for any subgroups, no economic subgroup analyses were conducted as part of this appraisal.

B.3.12 *Benefits not captured in the QALY calculation*

There are a number of benefits of tisagenlecleucel which are not explicitly captured in the QALY calculation, which, if included, would improve the cost-effectiveness of tisagenlecleucel further.

Tisagenlecleucel is a potentially curative therapy and therefore the QALY calculation may not fully capture the significant impact to patients of having a one-time treatment with curative potential.

In addition, as the bulk of clinical management for ALL is given in the outpatient setting, the majority of care is informal and provided by carers, most notably working parents. The impact of improved prognosis and curative potential of tisagenlecleucel is also expected to reduce the burden on carers for patients with ALL which is not captured in the QALY calculation.

Finally, the side-effect profile of tisagenlecleucel is more manageable than current treatment options, reducing the need for carers to manage troublesome side effects.

B.3.13 *Validation*

B.3.13.1 Validation of cost-effectiveness analysis

Two sets of clinical validation exercises were conducted, one as part of the original submission (TA554) and another as part of the current submission, with UK clinicians experienced in the treatment of pALL and ALL. Survival extrapolations, treatment pathway, generalisability of the evidence sources and the cost-effectiveness model inputs were validated during these exercises to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and therefore, outcomes predicted by the model being clinically plausible. Given the clinical validation teleconferences took place virtually during working hours, clinicians were compensated as per fair market value for attending the validation teleconferences and reviewing any pre-reading material.

During first clinical validation exercise performed as part of the original submission (TA554), expert clinical opinion was sought to validate the following:

- Treatment pathway
- Generalisability of efficacy data sources
- Economic model inputs which included:
    - Resource use and hospitalisation (length of stay)
    - AE rates
    - Subsequent allo-SCT rates
    - Utility values

- SMR
- Monitoring and follow-up
- Patient baseline characteristics

During the meeting, clinicians provided feedback verbally whereby clinicians were largely in agreement on the approaches and assumptions taken in the development of the cost-effectiveness model.

As part of the current submission, a second set of clinical validation teleconferences was performed with three UK clinical experts (existing or former NHS Haematologists) who were experienced in the treatment of r/r B-cell ALL and had the clinical experience of using tisagenlecleucel and other CAR-T therapies. There were no conflicts of interest declared with the UK clinical experts consulted. This validation exercise ensured that the cost-effectiveness analysis was reflective of current UK clinical practice while addressing concerns raised in the original appraisal (TA554). Prior to the second set of clinical validation teleconferences, clinicians were sent a pre-read slide deck containing the following:

- An overview of the current treatment options for Ph-ve r/r B-cell ALL patients
- An overview of ELIANA trial efficacy data from the latest data-cut (17th Nov 2022), including the latest Kaplan–Meier survival data

Using the information provided, clinical experts were asked to provide lower, upper and most likely estimates for the proportion of patients they would expect to be event-free and alive at 1, 2, 5, 10 and 20 years when receiving tisagenlecleucel. In the subsequent teleconference, the clinical experts were shown figures displaying the Kaplan–Meier data and the parametric survival models generated by their earlier responses. Survival estimates predicted by these models at various timepoints were also provided, as well as predicted cure fractions for the mixture cure models. Clinical experts were asked to indicate any extrapolations that they considered to be clinically implausible, as well as those that were preferred. Clinicians were also asked to provide lower, upper and a most likely estimate for the proportion of patients who would achieve a cure fraction for patients receiving tisagenlecleucel and all comparators, as well as estimates on the proportion of patients receiving allo-SCT after receiving different therapies. Of note, the clinicians provided an estimate for the mean number of cycles for treatment on blinatumomab, where the ERG had previously raised concerns in the original appraisal (TA554).[9] Clinicians also shared further details on AEs of special interest which included IVIg and CRS.

Opinions provided in both validation meeting exercises and those gathered after the meeting were recorded and written-up in the clinical validation meeting report provided in the reference pack accompanying this submission. Based on this report, key feedback from clinical experts has been presented and informed the economic modelling, where indicated in this submission.

B.3.13.2 Technical validation of cost-effectiveness analysis

The model programming was checked by a health economist who was not involved in the original development of the model using a validation checklist reported by Büyükkaramikli *et al.* 2019.[159] This involved a quality control check of the formulae used in the model and stress testing of the model to ensure that it behaves as expected when extreme values are used. The stress test checklist used to validate the model and the results of this test are presented in Table 88.

The results indicate that the model behaved as expected and passed all of the stress tests implemented. All changes to the model were made by a health economist, and each change made after the performance of the stress test checklist was fully quality controlled by a second health economist.

Table 81: Stress test checklist used for cost-effectiveness model validation

#	Test	Expected effect	Observed effect equivalent to expected effect?
1	Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0.	QALYs across all treatments should be equal.	As expected
2	Set mortality rate to 0% at all ages (and any other mortality in the model)	There are no deaths in the model.	As expected
3	Set mortality rate to 100% at all ages	All patients are dead in the first cycle.	As expected
4	Increase mortality rate	Costs are reduced.	As expected
5	Set the health state utilities the same for all states	Life years to QALY ratio should be the same across all treatments	As expected
6	Set the utilities for all health states to 0 and adverse events to 0 and set AE disutilities to 0	All QALYS = 0.	As expected
7	Set the cost and utility consequences for adverse events and discontinuation to 0, then undo these changes and set all adverse event rates to 0	Results in both cases are the same	As expected
8	Set adverse event and discontinuation rates to 0, then undo these changes and set adverse and discontinuation rates to a high level	The first scenario should result in lower costs, higher life years and greater QALYs than the second	As expected
9	Decrease the utilities for all health states simultaneously whilst keeping event-based utility decrements constant	QALYs are reduced	As expected
10	Set equal the effectiveness, utility and safety-related model inputs for all treatment options	No difference between LYs and QALYs for each treatment arm, at any given time	As expected
11	Set the costs of treatments to 0	All treatments costs = 0	As expected
12	Double the costs of treatments	Treatment costs doubled	As expected
13	Increase body weight and/or body surface area (only relevant for weight/BSA dependent dosing)	Treatment costs (for weight/BSA dependent treatments) are increased	As expected
14	Set all administration costs to 0	All administration costs = 0	As expected

15	Double all administration costs	Administration costs doubled	As expected
16	Turn off/on vial sharing	Costs should increase without vial sharing	As expected
17	Set all monitoring/follow-up costs to 0	Monitoring/follow-up costs = 0	As expected
18	Double all monitoring/follow-up costs	Monitoring/follow-up costs doubled	As expected
19	Alter the time horizon	Total costs and QALYS increase/decrease in accordance with longer/shorter horizons	As expected
20	Set discount rates to 0%	Undiscounted results = discounted results	As expected
21	Set discount rates to 100%	Costs and QALYs reduce significantly.	As expected
22	Run the deterministic/one-way sensitivity analysis and check all input parameters affect results when values are changed	Any input parameters should affect the incremental QALYS, costs or both (unless it has an exactly equal effect on all arms in the model)	As expected

Abbreviations: AE: adverse event; BSA: body surface area; QALY: quality-adjusted life years.
Source: Büyükkaramikli et al (2019).[159]

B.3.14 *Interpretation and conclusions of economic evidence*

The economic analysis conducted was based on an adaption of the *de novo* economic model developed for the original appraisal (TA554) evaluating the cost-effectiveness of tisagenlecleucel versus the relevant comparators in the UK for patients up to 25 years of age with r/r B-cell ALL. The *de novo* economic model presented in TA554 was considered appropriate for decision-making by the NICE committee and updated in the context of the current submission for tisagenlecleucel for routine commissioning in this indication. The population of the economic analysis considered paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse which reflects the patient populations of all three tisagenlecleucel clinical trials (ELIANA, ENSIGN and B2101J) and is consistent with patients included in the final NICE scope. This is with the exception of patients with Ph+ve disease, who comprise a very small minority (<3%) of the patient population. The paucity of evidence available for either tisagenlecleucel or any comparators means that a robust comparison was not possible in this small patient population for the purposes of this appraisal.

The comparators included within the economic analysis were blinatumomab and salvage chemotherapy (FLAG-IDA). These treatment options reflect the most relevant comparators currently licenced and being used in UK clinical practice for paediatric and young adult patients

up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. Furthermore, the economic analysis was conducted from the perspective of the UK NHS and PSS, and can therefore be considered directly applicable to clinical practice in England. Resource use assumptions have been validated with input from several UK clinical experts and costs included were all derived from UK sources (e.g. NHS Reference Costs, the BNF or the eMIT) where possible.[14]

Whilst there were no UK centres in the tisagenlecleucel clinical trials, the patient populations enrolled in the pivotal ELIANA trial include EU5 countries such as Germany and Spain and can be considered generalisable to the relevant patient population in the UK, based on clinical expert feedback gathered as part of the original appraisal (TA554).

Given the availability of data with long-term follow-up (79.4 months median follow-up from tisagenlecleucel infusion), survival for tisagenlecleucel in the economic model was based on the ELIANA trial alone, the pivotal trial that informed the marketing authorisation for tisagenlecleucel in this indication and the trial considered most generalisable to the intended patient population and use of tisagenlecleucel in UK clinical practice. The ELIANA trial results are corroborated by real-world treatment effectiveness of tisagenlecleucel during the managed access period as captured in the NHSE CDF Report, which show even better OS results than the ELIANA trial.[2, 3] Analyses based on long term data of the ELIANA trial mitigate concerns raised in the original appraisal (TA554) surrounding uncertainty in the extrapolation of OS for tisagenlecleucel and in turn, the curative potential of tisagenlecleucel,[9] with reduced variation observed in cure fractions predicted by mixture cure models fitted to the latest data-cut of the ELIANA trial (DCO 17th Nov 2022).

In addition, OS extrapolations were extensively validated by clinical experts experienced in the use of tisagenlecleucel in paediatric patients in UK clinical practice.[4] Finally, all three treatment options (i.e. tisagenlecleucel, blinatumomab and salvage chemotherapy [FLAG-IDA]) were modelled using a mixture-cure modelling approach to reflect the curative potential of subsequent allo-SCT, in line with the ERG's preference in TA554 and ensuring consistency and comparability across all modelled extrapolations.[9]

In terms of resource utilisation, where possible, all inputs were aligned to those previously accepted in the original appraisal (TA554). These inputs were sourced from UK publications, validated by clinical experts consulted as part of the original appraisal (TA554), and have been updated for the purposes of the current submission where relevant.[14]. An NHS tariff covering the cost of tisagenlecleucel administration was sourced from the NICE appraisal for brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (TA893).[58] This tariff represents the most up-to-date cost of treatment with a CAR-T therapy that is accepted by NICE and NHSE. It includes costs associated with the administration of tisagenlecleucel, covering leukapheresis, treatment administration, treatment adverse events, monitoring and training.

A limitation of the cost-effectiveness analysis which was raised by the ERG in the original appraisal (TA554) is the appropriateness of the use of efficacy for clofarabine monotherapy (Jeha *et al.* [2006]) to inform the effectiveness estimates for salvage chemotherapy (FLAG-IDA).[9] However, the Kuhlen *et al.* (2017) study suggested by the ERG has considerable limitations as a source of comparator efficacy data given inclusion of a higher proportion of patients in first relapse and the inclusion of patients with extramedullary relapse, and thus its potential to overestimate OS. SLRs conducted for the purposes of this submission identified no new trials

and hence, as per the original appraisal (TA554), a lack of published data to support this assumption of equivalence of effectiveness of these therapies in this patient population remains. However, clinical feedback gathered as part of the original submission was that this assumption was reasonable and that the efficacy between these therapies could be considered comparable in clinical practice.[14] The same efficacy source was also used in the NICE mock appraisal for regenerative therapies. Therefore, Jeha *et al.* (2006) was used as comparator data source for salvage chemotherapy in this submission as well. However, as noted above, mixture-cure models were explored to reflect the curative potential of patients receiving allo-SCT following salvage chemotherapy.

Finally, extensive scenario analyses were performed and showed the model to be robust to the majority of assumptions employed in the base case analysis. Overall, the results of the economic analysis indicate that tisagenlecleucel is cost-effective for patients up to 25 years of age with r/r B-cell ALL when compared with the treatment options most commonly used in these patients in the UK (blinatumomab and salvage chemotherapy [FLAG-IDA]). Tisagenlecleucel is associated with ICERs versus blinatumomab and salvage chemotherapy of £11,655 and £17,669 per QALY, respectively, at tisagenlecleucel PAS price inclusive of the x1.7 severity modifier. Considered in the context of a disease which affects such a young population with extremely poor prognosis that is further exacerbated with each subsequent relapse, where median OS with current routinely funded therapies ranges from 3 to 7.5 months, tisagenlecleucel offers patients the potential for a cure.

Given that tisagenlecleucel is an ATMP with curative potential, a non-reference case annual discount rate of 1.5% applied to both costs and QALYs has been considered. Tisagenlecleucel is associated with ICERs versus blinatumomab and salvage chemotherapy of £7,708 and £12,462 per QALY, respectively, at tisagenlecleucel PAS price inclusive of the x1.7 severity modifier and non-reference case discount of 1.5%. When considering tisagenlecleucel at PAS price and a cost-effectiveness threshold of £30,000 per QALY with the x1.7 severity modifier applied, the probability of tisagenlecleucel being cost-effective is [redacted] when compared to blinatumomab and [redacted] when compared to salvage chemotherapy.

Tisagenlecleucel is already an established treatment option for r/r B-cell ALL patients given the reduced need for subsequent transplants and potential associated toxicity, as indicated by clinical experts consulted as part of this submission.[4] Its use in NHS practice under the CDF has provided children, young adults, and their parents hope of curing a disease for which there are otherwise limited treatment options. Given the curative potential of tisagenlecleucel supported by the long-term follow-up data from the ELIANA trial, the cost-effectiveness analysis presents a compelling case for tisagenlecleucel to be considered for routine commissioning for the treatment of r/r B-cell ALL, and ensure paediatric patients continue to have access to tisagenlecleucel in the NHS.

References

1. National Institute for Health and Care Excellence. TA554: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. Available at: https://www.nice.org.uk/guidance/TA554. [Last accessed: 4 May 2023].
2. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (17th November 2022 data cut-off). Data on File. 2023.
3. NHS England. Tisagenlecleucel for treating relapsed or refractory Philadelphia negative and positive B-cell acute lymphoblastic leukaemia in people aged 25 years and under – data review, 2023.
4. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2023.
5. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Subjects with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (7th May 2018 data cut-off). Data on File. 2019.
6. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter study to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (24th May 2019 data cut-off). Data on File. 2019.
7. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34:4381-4389.
8. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol. 2006;24:1917-23.
9. National Institute for Health and Care Excellence. Committee Papers: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. Available at: https://www.nice.org.uk/guidance/ta554/evidence/committee-papers-pdf-6653240173 [Last accessed: 4 May 2023].
10. European Medicines Agency. Kymriah (tisagenlecleucel). Summary of Product Characteristics (SmPC). Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf [Last accessed: 14 April 2023].
11. National Institute for Health and Care Excellence. TA541: Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia. Available at: https://www.nice.org.uk/guidance/ta541. [Last accessed: 4 May 2023].
12. Laetsch TW, Maude SL, Rives S, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. J Clin Oncol. 2022;41:1664-1669.
13. Ceppi F, Duval M, Leclerc J-M, et al. Improvement of the Outcome of Relapsed or Refractory Acute Lymphoblastic Leukemia in Children Using a Risk-Based Treatment Strategy. PLoS One. 2016;11:e0160310.
14. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2018.
15. National Institute for Health and Care Excellence. Reviewing our methods for health technology evaluation: consultation. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/chte-methods-consultation [Last accessed: 1 August 2023]. 2020.
16. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Process and methods [PMG36]. Available at:

https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. [Last accessed: 21 July 2023].
17. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]: Final scope. Available at: https://www.nice.org.uk/guidance/gid-ta11381/documents/final-scope-2. [Last accessed: 16 August 2023]. 2023.
18. Porter DL, Kalos M, Zheng Z, et al. Chimeric antigen receptor therapy for B-cell malignancies. J Cancer. 2011;2:331.
19. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood. 2010;116:4099-4102.
20. Smith AJ, Oertle J, Warren D, et al. Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. J Cell Immunotherapy. 2016;2:59-68.
21. Paul S, Rausch CR, Nasnas PE, et al. Treatment of relapsed/refractory acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2019;17:166-175.
22. European Medicines Agency. Kymriah (tisagenlecleucel). An overview of kymriah and why it is authorised in the EU. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah [Last accessed: 14 April 2023].
23. Children with Cancer UK. Acute Lymphoblastic Leukaemia. Available at: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/acute-lymphoblastic-leukaemia/ [Last accessed: 4 May 2023].
24. Nguyen K, Devidas M, Cheng S-C, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22:2142-2150.
25. Pui C-H, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol. 2015;33:2938-2948.
26. Dana-Farber Cancer Institute. Relapsed Childhood Acute Lymphoblastic Leukemia. Available at: https://www.dana-farber.org/relapsed-childhood-acute-lymphoblastic-leukemia/#:~:text=Relapsed%20acute%20lymphoblastic%20leukemia%2C%20or,will%20have%20the%20disease%20return. [Last accessed: 14 April 2023].
27. Nebraska Hematology-Oncology (NHO). Refractory ALL. Available at: http://yourcancercare.com/types-of-cancer/leukemia/childhood-acute-lymphoblastic-leukemia/childhood-acute-lymphoblastic-leukemia-refractory [Last accessed: 4 May 2023].
28. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2009;28:648-654.
29. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia (Supplementary Appendix). N Engl J Med. 2018;378:439-448.
30. Kizilocak H, Okcu F. Late Effects of Therapy in Childhood Acute Lymphoblastic Leukemia Survivors. Turk J Haematol. 2019;36:1-11.
31. Sherief LM, Kamal NM, Abdalrahman HM, et al. Psychological impact of chemotherapy for childhood acute lymphoblastic leukemia on patients and uheir parents. Medicine (Baltimore). 2015;94:e2280.
32. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence by sex and UK country. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero [Last accessed: 4 May 2023].

33. Children's Cancer and Leukaemia Group. UK Acute Lymphoblastic Leukaemia (UKALL) 2019 Interim Guidelines. Available at: https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/UKALL_2019_Interim_Guidance_Final.pdf [Last accessed: 4 May 2023]. 2019.
34. Pan-London Blood Cancer. Pan-London Haemato-Oncology Clinical Guidelines. Acute Leukaemias and Myeloid Neoplasms. Part 1: Acute Lymphoblastic Leukaemia. Available at: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-ALL-Guidelines-Jan-2020.pdf [Last accessed: 4 May 2023]. 2020.
35. Children's Cancer and Leukaemia Group. Clinical treatment guidelines. Available at: https://www.cclg.org.uk/what-we-do/clinical-treatment-guidelines [Last accessed: 4 May 2023].
36. American Cancer Society. Chronic Lymphocytic Leukemia. Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html [Last accessed: 4 May 2023].
37. American Cancer Society. Acute Lymphocytic Leukemia. Available at: https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html [Last accessed: 4 May 2023].
38. Ravandi F, Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23:1043-63, vi.
39. Hettle R, Corbett M, Hinde S, et al. The Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: An Exploration of Methods for Review, Economic Evaluation and Appraisal. Health Technol Assess. 2017;21:1-204.
40. Leukemia and Lymphoma Society. Ph-positive ALL Therapy. Available at: https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment/ph-positive-all-therapy [Last accessed: 4 May 2023].
41. Koo HH. Philadelphia chromosome-positive acute lymphoblastic leukemia in childhood. Korean J Pediatr. 2011;54:106-110.
42. Cancer Research UK. About acute lymphoblastic leukaemia. Available at: http://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [Last accessed: 4 May 2023].
43. National Health Service (NHS). Acute lymphoblastic leukaemia. Available at: https://www.nhs.uk/Conditions/Leukaemia-acute-lymphoblastic/Pages/Introduction.aspx#symptoms [Last accessed: 4 May 2023].
44. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am. 2015;62:61-73.
45. Reismüller B, Peters C, Dworzak MN, et al. Outcome of children and adolescents with a second or third relapse of acute lymphoblastic leukemia (ALL): a population-based analysis of the Austrian ALL-BFM (Berlin-Frankfurt-Münster) study group. J Pediatr Hematol Oncol. 2013;35:e200-204.
46. Chen B, Zou Z, Zhang Q, et al. Efficacy and safety of blinatumomab in children with relapsed/refractory B cell acute lymphoblastic leukemia: A systematic review and meta-analysis. Front Pharmacol. 2022;13:1032664.
47. Fardell JE, Vetsch J, Trahair T, et al. Health-related quality of life of children on treatment for acute lymphoblastic leukemia: A systematic review. Pediatr Blood Cancer. 2017;64.
48. Essig S, von der Weid NX, Strippoli MP, et al. Health-related quality of life in long-term survivors of relapsed childhood acute lymphoblastic leukemia. PLoS One. 2012;7:e38015.
49. Pagano E, Baldi I, Mosso ML, et al. The economic burden of caregiving on families of children and adolescents with cancer: A population-based assessment. Pediatr Blood Cancer 2014;61:1088-1093.

50. Ren Y, Li X. Direct and indirect costs of families with a child with acute lymphoblastic leukaemia in an academic hospital in China: a cross-sectional survey. BMJ Open. 2019;9:e030511.
51. Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v69-v82.
52. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Available at: https://jnccn.org/view/journals/jnccn/19/9/article-p1079.xml [Last accessed: 4 May 2023]. J Natl Compr Canc Netw. Volume 19.
53. National Institute for Health and Care Excellence. TA450: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. Available at: https://www.nice.org.uk/guidance/ta450. [Last accessed: 4 May 2023].
54. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010;376:2009-2017.
55. European Medicines Agency. BLINCYTO (blinatumomab) 38.5 micrograms powder for concentrate and solution for solution for infusion. Summary of Product Characteristics (SmPC). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003731/WC500198228.pdf [Last accessed: 1 June 2023].
56. European Medicines Agency. Summary of product characteristics (SmPC): BESPONSA (Inotuzumab ozogamicin). Available at: https://www.ema.europa.eu/en/documents/product-information/besponsa-epar-product-information_en.pdf [Last accessed: 4 May 2023].
57. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-847.
58. National Institute for Health and Care Excellence. TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. Available at: https://www.nice.org.uk/guidance/ta893. [Last accessed: 21 June 2023].
59. ClinicalTrials.gov. ELIANA (NCT02435849). Available at: https://clinicaltrials.gov/ct2/show/NCT02435849 [Last accessed: 1 May 2023].
60. ClinicalTrials.gov. ENSIGN (NCT02228096). Available at: https://clinicaltrials.gov/ct2/show/NCT02228096 [Last accessed: 1 May 2023].
61. ClinicalTrials.gov. B2101J (NCT01626495). Available at: https://clinicaltrials.gov/ct2/show/NCT01626495?term=PEDI-CART&rank=1 [Last accessed: 1 May 2023].
62. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (30th January 2017 data cut-off). Data on File. 2017.
63. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (13th April 2018 data cut-off). Data on File. 2018.
64. Maude SL, Pulsipher MA, Boyer MW, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis: Am Soc Hematology., 2016.
65. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-17.

66. Gajjar A, Harrison PL, Sandlund JT, et al. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. Blood. 2000;96:3381-4.
67. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (25th April 2017 data cut-off). Data on File. 2017.
68. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (31st December 2017 data cut-off). Data on File. 2017.
69. GRACE principles: a validated checklist for evaluating the quality of observational cohort studies for decision-making support. Available at: https://www.graceprinciples.org/doc/GRACE-Checklist-v5.1.pdf [Last accessed: 15 February 2018].
70. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (6th October 2017 data cut-off). Data on File. 2017.
71. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (Supplementary Appendix; 30th January 2017 data cut-off). Data on File. 2017.
72. Grupp SA, Maude SL, Rives S, et al. Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: Updated Analysis of the ELIANA Clinical Trial. Biol Blood Marrow Transplant. 2019;25:S126-127.
73. Grupp SA MS, Rives S, Baruchel A, Boyer MW, Bittencourt H, Bader P, Büchner J, Laetsch TW, Stefanski H, Myers GD, Qayed M, Pulsipher, MA, De Moerloose B, Yanik GA, Davis KL, Martin PL Nemecek ER, Peters C, Hiramatsu H. Updated Analysis of the Efficacy and Safety of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory (r/r) Acute Lymphoblastic Leukemia. Blood. 2018;132:895-895.
74. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (17th Aug 2016 data cut-off). Data on File. 2016.
75. Belin L, Tan A, De Rycke Y, et al. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. Br J Cancer. 2020;122:1707-1714.
76. Innes AJ, Woolley P, Szydlo R, et al. Complete Remission with Incomplete Count Recovery (CRi) Prior to Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia Is Associated with a High Non-Relapse Mortality without Increased Relapse Risk. Blood. 2018;132:4650.
77. Hills RK, Thomas I, Burnett AK, et al. The Achievement of Complete Remission Is Associated with Improved Quality of Life in Non-Intensively Treated Patients with Acute Myeloid Leukemia: Results of the UK NCRI LI-1 Tria. Blood. 2018;132:372.
78. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:7-12.
79. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378:439-448.
80. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia (Trial Protocol). N Engl J Med. 2018;378:439-448.

81. Delgado A, Guddati AK. Clinical endpoints in oncology - a primer. Am J Cancer Res. 2021;11:1121-1131.
82. Ewing JE, King MT, Smith NF. Validation of modified forms of the PedsQL generic core scales and cancer module scales for adolescents and young adults (AYA) with cancer or a blood disorder. Qual Life Res. 2009;18:231-44.
83. Kimman ML, Dirksen CD, Lambin P, et al. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. Health Qual Life Outcomes. 2009;7:11.
84. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res. 2010;19:875-86.
85. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3:329-41.
86. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
87. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D: Springer, 2014.
88. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39:800-12.
89. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (1st February 2016 data cut-off). Data on File. 2016.
90. Gore L, Locatelli F, Zugmaier G, et al. Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Blood Cancer J. 2018;8:80.
91. Locatelli F, Zugmaier G, Rizzari C, et al. Improved survival and MRD remission with blinatumomab vs. chemotherapy in children with first high-risk relapse B-ALL. Leukemia. 2022;37:222-225.
92. Bertaina A, Vinti L, Strocchio L, et al. The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukaemia of childhood. Br J Haematol. 2017;176:629-636.
93. Zwaan CM, Kowalczyk J, Schmitt C, et al. Safety and efficacy of nelarabine in children and young adults with relapsed or refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of a phase 4 study. Br J Haematol. 2017;179:284-293.
94. Kuhlen M, Willasch AM, Dalle JH, et al. Outcome of relapse after allogeneic HSCT in children with ALL enrolled in the ALL-SCT 2003/2007 trial. Br J Haematol. 2018;180:82-89.
95. Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Blood 2011;118:6043-6049.
96. Miano M PA, Putti MC, Dufour C, Messina C, Barisone E, Ziino O, Parasole R, Luciani M, Lo Nigro L, De Rossi G, Varotto S, Bertorello N, Petruzziello F, Calvillo, M, , C. M. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma. 2012;53:1693-1698.
97. Cooper TM, Razzouk BI, Gerbing R, et al. Phase I/II trial of clofarabine and cytarabine in children with relapsed/refractory acute lymphoblastic leukemia (AAML0523): a report from the Children's Oncology Group. Pediatr Blood Cancer. 2013;60:1141-1147.
98. Locatelli F, Testi AM, Bernardo ME, et al. Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. Br J Haematol. 2009;147:371-8.

99. Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood. 2012;120:285-290.
100. ClinicalTrials.gov. CAR-T Long Term Follow Up (LTFU) Study (PAVO) (NCT02445222). Available at: https://clinicaltrials.gov/ct2/show/NCT02445222 [Last accessed: 1 May 2023].
101. Food and Drug Adminstration. FDA approval brings first gene therapy to the United States. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm [Last accessed: 1 June 2023].
102. Novartis Pharmaceuticals Ltd. Novartis granted US FDA Priority Review for Kymriah(TM) (tisagenlecleucel), formerly CTL019, for adults with r/r DLBCL. Available at: https://www.novartis.com/news/media-releases/novartis-granted-us-fda-priority-review-kymriahtm-tisagenlecleucel-formerly-ctl019-adults-rr-dlbcl [Last accessed: 1 June 2023].
103. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: A meta-analysis. JAMA Oncol. 2017;3:e170580.
104. Raetz EA, Borowitz MJ, Devidas M, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study[corrected]. J Clin Oncol. 2008;26:3971-8.
105. Phillippo D, Ades T, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available at: https://research-information.bris.ac.uk/ws/portalfiles/portal/94868463/Population_adjustment_TSD_FINAL.pdf [Last accessed: 1 June 2023].
106. Kelly MJ, Pauker SG, Parsons SK. Using nonrandomized studies to inform complex clinical decisions: the thorny issue of cranial radiation therapy for T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer. 2015;62:790-7.
107. Carey N, Leahy J, Trela-Larsen L, et al. Tisagenlecleucel for relapsed/refractory acute lymphoblastic leukemia in the Irish healthcare setting: cost-effectiveness and value of information analysis. Int J Technol Assess Health Care. 2022;38:e56.
108. Carey N. POSB125 The Impact of Discounting on the Cost Effectiveness of Tisagenlecleucel for Relapsed/Refractory Acute Lymphoblastic Leukaemia. Volume 25: ISPOR Value in Health., 2022:S85-S86.
109. Thielen FW, van Dongen-Leunis A, Arons AMM, et al. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. Eur J Haematol. 2020;105:203-215.
110. Ribera Santasusana JM, de Andrés Saldaña A, García-Muñoz N, et al. Cost-Effectiveness Analysis of Tisagenlecleucel in the Treatment of Relapsed or Refractory B-Cell Acute Lymphoblastic Leukaemia in Children and Young Adults in Spain. Clinicoecon Outcomes Res. 2020;12:253-264.
111. Scottish Medicines Consortium. Tisagenlecleucel (Kymriah). Available at: https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-fullsubmission-smc2129/. [Last accessed: 1 June 2023]. 2019.
112. Haute Autorité de Santé. BLINCYTO (blinatumomab) OPINIONS ON DRUGS - Economic opinion. Available at: https://has-sante.fr/jcms/p_3349491/en/blincyto-blinatumomab [Last accessed: 1 June 2023]. 2022.
113. Moradi-Lakeh M, Yaghoubi M, Seitz P, et al. Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland. Adv Ther. 2021;38:3427-3443.

114. Norwegian Medicines Agency (NoMA). Single technology assessent: Tisagenlecleucel (Kymriah) for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients. Available at: https://nyemetoder.no/Documents/Rapporter/Tisagenlecleucel%20(Kymriah)%20-%20hurtig%20metodevurdering.pdf [Last accessed: 1 June 2023]. 2018.
115. Lis J, Kawalec, P., Glasek, M. Economic evaluation of acute lymphoblastic leukaemia treatment with clofarabine (Evoltra®) combined with chemotherapy for children and adolescents in Poland. Journal of Health Policy and Outcomes Research. 2012.
116. National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template, process and methods [24]. Available at: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333. [Last accessed: 20 June 2023].
117. Tyagarajan S, Spencer T, Smith J. Optimizing CAR-T Cell Manufacturing Processes during Pivotal Clinical Trials. Mol Ther Methods Clin Dev. 2020;16:136-144.
118. National Institute for Health and Care Excellence. The NICE methods of health technology evaluation: the case for change. Available at: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.nice.org.uk%2FMedia%2FDefault%2FAbout%2Fwhat-we-do%2Four-programmes%2Fnice-guidance%2Fchte-methods-consultation%2FNICE-methods-of-health-technology-evaluation-case-for-change.docx&wdOrigin=BROWSELINK [Last accessed: 1 August 2023]. 2020.
119. MacArthur AC, Spinelli JJ, Rogers PC, et al. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. Pediatr Blood Cancer. 2007;48:460-7.
120. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med 2016;375:740-53.
121. Drugs and pharmaceutical electronic market information (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. [Last accessed: 1 August 2023].
122. National Health Service England (NHS). NHS Reference Costs 2021-2022. National Schedule of NHS Costs 2021/22: the main schedule. Available at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ [Last accessed: 21 June 2023].
123. British National Formulary (BNF). Available at: https://bnf.nice.org.uk/. [Last accessed: June 2023].
124. NHS Network Site Specific Group (NSSG) - Haematology. Myeloid Group - FLA-IDA. 2017. Available at: http://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-9-fla-ida.pdf. [Last accessed: 1 June 2023].
125. CRD and CHE Technology Assessment Group University of York. Exploring the assessment and appraisal of regenerative medicines and cell therapy products. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/final-york-report-march-16.pdf. [Last accessed: 21 Jun 2023]. 2016.
126. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at: https://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/survival-analysis-tsd/. [Last accessed: 1 July 2023].
127. ISPOR Estimating the Long-Term Outcomes Associated With ImmunoOncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Available at: https://www.ispor.org/publications/journals/value-outcomes-spotlight/abstract/january-february-

2018/estimating-the-long-term-outcomes-associated-with-immuno-oncology-therapies-challenges-and-approaches-for-overall-survival-extrapolations [Last accessed: 1 June 2023].
128. Rutherford J LP, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, Latimer NR. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Available at https://www.sheffield.ac.uk/nice-dsu/tsds/flexible-methods-survival-analysis. [Last accessed: 30 June 2023]. 2020.
129. ISPOR Glasgow, Workshop 11: Determining the Value of Long-term Outcomes Associated with Immuno-oncology Therapies - Challenges and Approaches for OS Extrapolations. Available at: https://www.ispor.org/Event/ReleasedPresentations/2017Glasgow#workshoppresentations [Last accessed May 2018].
130. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Technology appraisal guidance [TA872]. Available at: https://www.nice.org.uk/guidance/ta872. [Last accessed: 1 August 2023]. 2023.
131. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy. Technology appraisal guidance [TA895]. Available at: https://www.nice.org.uk/guidance/ta895. [Last accessed: 1 August 2023]. 2023.
132. Office for National Statistics. Interim Life Tables: England & Wales Period expectation of life based on data for the years 2018-2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/interimlifetablesenglandandwales [Last accessed: 22 April 2023].
133. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
134. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med. 2016;374:833-42.
135. Socié G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med. 1999;341:14-21.
136. Bhatia S, Robison LL, Francisco L, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. Blood. 2005;105:4215-22.
137. Hettle R, Corbett M, Hinde S, et al. Exploring the assessment and appraisal of regenerative medicines and cell therapy products. NIHR HTA Programme. 2015;14:06.
138. Schlenk RF, Döhner H, Döhner K, et al. Event-free survival is a surrogate for overall survival in patients treated for acute myeloid leukemia: Am Soc Hematology., 2015.
139. EuroQol. EQ-5D-Y (Youth). Available from: https://euroqol.org/eq-5d-instruments/eq-5d-y-about/. [Last accessed: 1 August 2023].
140. EuroQol. EQ-5D-Y | Valuation. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-y-about/valuation/. [Last accessed: 21 Jun 2023].
141. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35:1095-108.
142. Aristides M, Barlev A, Barber B, et al. Population preference values for health states in relapsed or refractory B-precursor acute lymphoblastic leukemia in the United Kingdom. Health Qual Life Outcomes. 2015;13:181.
143. Sung L, Buckstein R, Doyle JJ, et al. Treatment options for patients with acute myeloid leukemia with a matched sibling donor: a decision analysis. Cancer. 2003;97:592-600.

144. Office for National Statistics. Health Survey for England, 2014. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2014. [Last accessed: 4 July 2023].
145. British National Formulary (BNF) Online. Blinatumomab. Available at: https://bnf.nice.org.uk/drugs/blinatumomab-specialist-drug/. [Last accessed: 1 July 2023].
146. British National Formulary (BNF) Online. Idarubicin. Available at: https://bnf.nice.org.uk/medicinal-forms/idarubicin-hydrochloride.html. [Last accessed: 1 July 2023].
147. National Health Service (NHS) Blood and Transplant. UK Stem Cell Strategy Oversight Committee. Unrelated Donor Stem Cell Transplantation in the UK: Effective Affordable Sustainable. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/29047/unrelated-donor-stem-cell-transplantation-in-the-uk-2014.pdf [Last accessed: 1 June 2023]. 2014.
148. Personal Social Services Research Unit. Hospital and community health services (HCHS) index. Available at: https://www.pssru.ac.uk/pub/uc/uc2017/sources-of-information.pdf. [Last accessed: 1 June 2023].
149. National Cancer Comprehensive Network. Pediatric Acute Lymphoblastic Leukemia Guidelines. Available at: https://www.nccn.org/patients/guidelines/content/PDF/ped_all_patient.pdf [Last accessed: 25 April 2023]. 2023.
150. Campbell K. Childhood Acute Lymphoblastic Leukaemia (ALL) (and teenagers and young adults up to 24 years old). Revised October 2011. Available at: http://leukaemialymphomaresearch.org.uk/sites/default/files/childhood_all_oct_2011.pdf. [Last accessed: November 2017].
151. National Institute for Health and Care Excellence. Committee Papers: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia [TA450]. Available at: https://www.nice.org.uk/guidance/ta450/documents/committee-papers [Last accessed: 30 June 2023].
152. British National Formulary (BNF) Online. Flebogamma (IVIG) DIF 20g/200mL and 500mg/10mL solution for infusion. Available at: https://bnf.nice.org.uk/medicinal-forms/normal-immunoglobulin.html [Last accessed: 1 July 2023]. .
153. Schneider P, McNamara S, Love-Koh J, et al. QALY Shortfall Calculator. 2022. Available at: https://shiny.york.ac.uk/shortfall. [Last accessed: 17 August 2023]. 2021.
154. Office for National Statisitics. National life tables - life expectancy in the UK: 2018 to 2020. 2021. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020#:~:text=Across%20the%20UK%2C%20life%20expectancy,years%20for%20females%20in%20Northern. [Last accessed: 1 May 2023].
155. Hernández MA, Pudney S, Wailoo A. NICE DSU Report: Estimating EQ-5D by age and sex for the UK. Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d. [Last accessed: 1 September 2023]. 2022.
156. Pennesi E, Michels N, Brivio E, et al. Inotuzumab ozogamicin as single agent in pediatric patients with relapsed and refractory acute lymphoblastic leukemia: results from a phase II trial. Leukemia. 2022;36:1516-1524.
157. Phillippo DM, Ades AE, Dias S, et al. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making. 2018;38:200-211.
158. Ren S, Minton J, Whyte S, et al. A New Approach for Sampling Ordered Parameters in Probabilistic Sensitivity Analysis. Pharmacoeconomics. 2018;36:341-347.

159. Buyukkaramikli NC, Rutten-van Molken M, Severens JL, et al. TECH-VER: A verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics. 2019;37:1391-1408.

Appendices

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
Tisagenlecleucel in rr B-cell ALL_SIP [NoCON]	N/A	No	October 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name)

Generic name: Tisagenlecleucel; **Brand name:** Kymriah®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is children (**paediatric**) and young adult patients up to 25 years of age with **B-cell acute lymphoblastic leukaemia (ALL)** that is **refractory**, in **relapse post-transplant** or in second or later relapse.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **European Medicines Agency (EMA)** have approved tisagenlecleucel as a treatment for children (paediatric) and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse (1). More information on this can be found in **Document B** in **Section B.1.2.**[a]

NICE Previous Cancer Drugs Fund (CDF) Recommendation

Tisagenlecleucel had previously been reviewed by NICE in 2018 and was approved for use through the **Cancer Drugs Fund (CDF)** until 2023 (2). When a drug is available for use via the CDF, people can be treated with the drug in NHS hospitals for a set time period while more data is collected on how well the drug works. Once more data is collected, a decision is made on whether the drug should remain available for routine use in the NHS hospitals.

The purpose of this submission is to evaluate whether tisagenlecleucel should be approved for routine funding under the NHS and therefore, continue to remain available for use in this population.

[a]**Please note**: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **teal**.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Novartis Pharmaceuticals UK Ltd has provided the following since 2020:

- Grant funding to Blood Cancer Alliance for the Blood Cancer Action plan: £45,380
- Grant funding for Support to Blood Cancer Alliance: £15,000
- Grant funding for a project for Leukaemia Care early diagnosis: £50,000
- Grant funding to Blood Cancer Alliance: £25,000
- Sponsorship for Leukaemia Care (UnicornFest): £15,000

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is B-cell ALL?

ALL is a rare type of blood cancer that starts from white blood cells called **lymphocytes** which normally help to fight infections in the body (3). In ALL, lymphocytes that have not fully developed, known as **lymphoblasts**, become cancerous and are overproduced, gathering in the bone marrow where new blood cells are made. ALL progresses quickly (within months) and is one of the most common cancers to affect children and young adults.

ALL can be grouped as either **B-cell** or **T-cell** ALL, with B-cell ALL being more common in children (4). ALL can also be further categorised based on the presence or absence of a **genetic abnormality** called the **Philadelphia (Ph) chromosome.** The majority of people with ALL do not have this chromosome, and are therefore diagnosed with Philadelphia-negative (Ph-ve) ALL (5).

What are the signs and symptoms of ALL?

ALL is a blood cancer (**leukaemia**) which affects the normal function of bone marrow to make healthy red blood cells and blood-clotting cells (**platelets**). People with B-cell ALL have a shortage of normal blood cells and a weaker **immune system** (6). Some symptoms include (6):

- Weight loss, fever, night sweats and loss of appetite
- Bruising – this is caused by a low number of blood-clotting cells (platelets)
- **Anaemia** – this is caused by a low number of red blood cells

ALL may sometimes spread and affect other areas of the body, resulting in the build-up of leukaemia cells and symptoms such as:

- Enlarged liver and **spleen**
- Lumps under the skin as a result of enlarged **lymph nodes**
- Bone and joint pain

How many people get ALL?

Approximately 800 people were diagnosed with ALL every year in the UK from 2016 to 2018 (7). 63% of people with ALL were children and young adults aged between 0 to 24 years (7). ALL is more common in younger people and accounts for 78% of all childhood leukaemia and almost one-third of all childhood cancers (3).

What is relapsed or refractory (r/r) B-cell ALL?

The disease is known as relapsed ALL when people experience a period of time in **remission** where the disease responds to treatment, but leukaemia cells then reappear, known as a relapse (8). When the disease does not respond to treatment, the disease is known as refractory ALL (8).

What is the impact of B-cell r/r ALL?

Disease overview

When people are first diagnosed with ALL, they receive **chemotherapy** treatment. Approximately 80% to 85% of people respond to this treatment and their body is successfully cleared of leukaemia cells (9, 10). However, 15% to 20% of people who had initially responded to the chemotherapy treatment would experience a relapse (11, 12). This tends to happen within two years of people with ALL receiving the initial chemotherapy treatment.

When people with ALL experience relapse, their chances of responding to another treatment decreases and hence, affects how long they live after receiving treatment (13). Treatment options available for patients at each disease phase are summarised below in **Section 2c**. With current treatment options, studies have estimated that people with r/r ALL are only expected to live for 3 to 7.5 months (14, 15).

Physical and emotional impact

People with ALL can experience various physical impacts. In people with ALL, leukaemia cells gather and take up space in the bone marrow (6). As a result, the bone marrow is unable to make as many normal blood cells required by the body (6). Most symptoms experienced by people with ALL are hence due to the reduced number of normal blood cells or blood-clotting cells (6). These symptoms include fatigue, anaemia and bruising (6). Cancer-related fatigue is a common symptom experienced by children with ALL and interferes with daily activities due to lower energy levels (16, 17).

Treatment for ALL is also associated with side-effects that can have both physical and psychological impact on people with ALL. A study which looked at children with ALL undergoing treatment found that children had more disrupted sleep, lower physical activity levels and felt more tired compared to other children who did not have ALL (18). Similarly, another study which looked at children with ALL undergoing chemotherapy found that they had a low level of self-esteem (19). Children who had ALL for a longer period of time had lower levels of self-esteem, suggesting that the psychological impact is influenced by the duration that people have the disease (19).

Quality of life

The impact on physical and emotional health can affect people with ALL's **quality of life**. The young age at which people are diagnosed with ALL and undergo treatment has been associated with a lasting impact due to factors such as disruption in education (20). People with relapsed ALL may experience late treatment effects, with those who are in

remission following a previous relapse perceiving themselves to have worse health than those who are in remission without a previous relapse (21). The late treatment effects experienced by people with ALL is further elaborated in **Section 2d**.

Impact on families and carers

As a disease that affects children and young adults, those who care for people with ALL spend a lot of time providing medical, practical and emotional support (19). This can impact their quality of life due to increased distress, depression, anxiety, stress or emotional pressures (19). People with ALL require regular visits to hospital, which can often disrupt parents' or caregivers' employment, resulting in reduced working hours and potentially increasing the financial impact felt by families and carers (22, 23). Younger parents and unemployed mothers of children with ALL were found to experience higher stress levels (19). High stress levels experienced by some parents may also affect their other personal relationships (19). The diagnosis of ALL therefore not only impacts people with ALL but also has a widespread impact on their families and carers.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is ALL diagnosed?

Preliminary tests for the diagnosis of ALL include a **complete blood count** test which shows the number of red blood cells, white blood cells and platelets in a person's blood (24). This is followed by a **peripheral blood smear** where a blood sample is taken and viewed under a microscope to count blood cells and check for abnormality in cell appearance (24). Diagnosis of ALL is then usually confirmed with a **bone marrow biopsy** (24). This may be done under local or general **anaesthetic** whereby a bone marrow liquid sample is taken from the patient and sent to a laboratory for testing (24).

Phases

ALL does not have a standard staging system unlike most other cancers (25). Staging refers to a common process of determining the extent and amount of cancer that has spread to other parts of the body (25). ALL is instead categorised into the following phases (25):

- Untreated: the cancer is newly diagnosed and awaits treatment
- In remission: the cancer responded to treatment
- Relapsed: the cancer came back after initial response to treatment and reaching remission
- Refractory: the cancer did not respond to treatment

Further details on the phases of ALL can be found here: Staging acute lymphoblastic leukemia | Canadian Cancer Society (25).

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for B-cell ALL?

The aim of treatment for ALL is to control symptoms and achieve **complete remission**. Complete remission is achieved when patients have normal blood cell counts, have a low number of leukaemic cells (referred to **minimal residual disease [MRD]**) and lymphoblasts are not detected elsewhere in the body. Treatment options at each phase of the disease offered to patients are summarised below.

Newly diagnosed disease

Children and young adults who are newly diagnosed with r/r B-cell ALL in the UK are typically entered into experimental **clinical trials**, if available (26). Otherwise, people with ALL are treated with multi-drug chemotherapy based on their cancer risk levels (27). The most common combination of chemotherapy includes three to four of the following drugs: dexamethasone, vincristine, asparaginase and daunorubicin (27). The chemotherapy consists of five phases in total and is given to people in hospitals (27). The treatment is usually given by an injection into a vein (**intravenously**) (27).

Primary refractory disease

If people do not respond to the chemotherapy treatment, they are given other treatment options which include **blinatumomab** and **inotuzumab ozogamicin** (*licensed in adults aged 18 years and over*)**.** These are both **targeted cancer drugs** called **monoclonal antibodies** that identify leukaemia cells in the body and kill cancer cells (27). If these options are unavailable, people may receive **salvage chemotherapy**, typically including the following drugs: fludarabine, cytarabine, granulocyte colony stimulating factor and idarubicin (FLAG-IDA) (27). Salvage chemotherapy refers to chemotherapy given to people with ALL when the disease does not respond to previous treatments.

People who achieve complete remission may subsequently receive an **allogenic stem cell transplant (allo-SCT)**. Achieving complete remission is a requirement for people with ALL to receive an allo-SCT. The aim of allo-SCT is to replace a person with ALL's stem cells with new healthy stem cells taken from a **donor** (28). An allo-SCT donor refers to a person, sometimes a brother or sister, from whom blood is taken to collect stem cells (28). These healthy donor stem cells are then infused into people with ALL whose disease is in

complete remission (29). The healthy stem cells travel to the bone marrow to make new healthy blood cells to fight against any leukaemia cells left in the body (28).

People who achieve complete remission after receiving inotuzumab ozogamicin may also be treated with **tisagenlecleucel**, which is a type of **chimeric antigen receptor T-cell (CAR-T)** therapy. In CAR-T therapy, a person with ALL's **immune cells** are removed, **genetically modified** to recognise cancer cells and re-infused to then attack the cancer cells (24). Further details on how CAR-T therapy works can be found below in **Section 3a**.

First relapse

If people with ALL experience a relapse following initial chemotherapy treatment, similar to those with refractory disease, treatment options include blinatumomab or inotuzumab ozogamicin (30, 31). People younger than 18 years may also be treated with another round of chemotherapy (32). If the disease goes into complete remission following this treatment, some patients receive **maintenance chemotherapy** treatment. The aim of maintenance chemotherapy is to prevent or delay another relapse. People with ALL who have achieved complete remission may also receive an allo-SCT.

Second relapse or relapse post-transplant

For people who experience another relapse after maintenance chemotherapy or allo-SCT, or relapse before allo-SCT, there are no further treatment options beyond those received previously. In general, treatments would not be offered again if patients have relapsed on these treatments previously. Treatment options for patients who have relapsed twice or relapsed before allo-SCT may include tisagenlecleucel, blinatumomab and salvage chemotherapy (33). With treatment options such as blinatumomab and salvage chemotherapy, people with ALL may not achieve complete remission and therefore, may be unable to receive an allo-SCT. Allo-SCT is also associated with potential toxicity and may be avoided in this treatment phase. Tisagenlecleucel (available via the CDF) is therefore commonly considered in the treatment phase, providing a potentially curative treatment option whilst reducing the need for a subsequent allo-SCT.

Tisagenlecleucel

In this submission, tisagenlecleucel is placed as a treatment option for children and young adult patients aged up to 25 years with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

r/r B-cell ALL from the patient perspective

The young age of diagnosis for people with r/r B-cell ALL means that they may have to undergo treatment during pivotal stages of their lives where they are still developing (20). As a result, long-term and late effects of treatment are often observed for people who have received treatment for childhood leukaemia or **lymphoma** (34). Long-term effects refer to medical issues that remain for months or years even after the treatment ends, whilst late effects refer to medical issues that do not appear until years after treatment has ended (34). Examples of long-term and late effects of treatment include having a lower attention span, poor memory or taking longer to process information (34). All of these effects can have an impact on long-term socioeconomic outcomes and quality of life, as elaborated below (34).

A study that included children with ALL undergoing chemotherapy reported that 85% of children had low level of self-esteem (20). This was found to be correlated with the duration of disease, which means the longer the duration of disease, the lower the self-esteem people experienced (20). Parents of these children also understandably reported high levels of distress and low moods whilst their children were undergoing treatment for ALL (20).

Another study compared the socioeconomic outcomes of ALL survivors in the United States and Canada with that of their siblings (35). This study found that ALL survivors had significantly lower rates of marriage, college graduation and health insurance coverage compared to their siblings, indicating that ALL and its treatment can have a profound impact on people's lives even after recovery (35).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment? Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Tisagenlecleucel is a CAR T-cell treatment. CAR T-cell treatments are made from a person's white blood cells, called T-cells. T-cells can recognise and target infected cells, or cancer cells, for clearance. T-cells are selective, so that they are tolerant to the body's own cells but can be very sensitive to **antigens** present on infected or cancer cells. They can directly attack infected or cancerous cells and activate other cells in the immune system. T-cells are taken from a person's blood and genetically modified to make CAR T-cells. These CAR T-cells are designed to recognise and target a specific **protein** found on cancer cells called CD19. Tisagenlecleucel is then infused (given intravenously) back into the person's blood, where the CAR T-cells find and kill cancer cells. By using the person's own immune system, tisagenlecleucel acts as a 'living drug' that can provide a long-lasting response. Tisagenlecleucel is given as a 'one-time' infusion and the process of creating CAR T-cells takes just several weeks, unlike other treatments which require multiple infusions over a longer time period. Tisagenlecleucel has been offered as a treatment option for paediatric and young adult patients with r/r B-cell ALL in the UK since late 2018 and has shown the potential to cure ALL for some patients (36). Further information about CAR T-cell treatment can be found at Cancer Research UK (CAR T-cell therapy | Cancer Research UK) (37).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Tisagenlecleucel is not intended to be used with any other treatment for ALL.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Tisagenlecleucel is given to patients in the following steps: **Collection of blood to manufacture tisagenlecleucel** • As tisagenlecleucel is made from a person's white blood cells, blood is collected using a catheter (small tube) placed in the vein • T-cells are then separated from the rest of the blood in a process called **leukapheresis** • This process can take 3 to 6 hours and may need to be repeated • The collected white blood cells are frozen and sent to the manufacturing site to make tisagenlecleucel which may take 3 to 4 weeks • In cases whereby tisagenlecleucel cannot be successfully manufactured, doctors would follow up to discuss the next step **Bridging treatment** • While tisagenlecleucel is being manufactured, patients are given chemotherapy treatments to stabilise their disease and prevent it from worsening **Lymphodepleting chemotherapy** • Shortly before the tisagenlecleucel infusion, patients are given a type of a treatment called **lymphodepleting chemotherapy** (also known as conditioning chemotherapy) over a few days. This decreases the number of T-cells in the patient's body to make room for the new CAR T-cells to grow once infused • This chemotherapy regimen usually consists of **fludarabine** and **cyclophosphamide** and is administered intravenously

Pre-medication

- Approximately 30 to 60 minutes before the infusion, patients are given medication to reduce the likelihood of any **side effects** to the infusion
- The pre-medication usually consists of **paracetamol**, **diphenhydramine** or an **antihistamine**

Infusion

- Prior to the infusion, the patient undergoes a series of assessments to ensure that the patient is well enough to receive the infusion of tisagenlecleucel
- Tisagenlecleucel is infused into the patient's blood. This usually takes less than 1 hour, during which the patient would closely monitored
- Following the infusion, doctors and nurses monitor patients closely for at least 4 weeks to check if the treatment is working and to control any side effects

Another resource that has further information on how tisagenlecleucel is given/taken is the Patient Information Leaflet (Kymriah, INN-tisagenlecleucel (medicines.org.uk)) (38).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of tisagenlecleucel in r/r B-cell ALL

A total of three clinical trials have studied tisagenlecleucel for the treatment of paediatric and young adult patients with r/r B-cell ALL. These include ELIANA (NCT02435849), ENSIGN (NCT02228096) and B2101J (NCT01626495), with the ELIANA trial being the main source of evidence (39-41).

All three trials are completed **single-arm**, **open-label** trials, which means that all participants knew and received tisagenlecleucel, and no **control treatment** was included. The three studies looked at how well tisagenlecleucel worked to treat tisagenlecleucel (its **efficacy**) and how safe the medicine was. The ELIANA trial also looked at the impact of tisagenlecleucel on patients' quality of life.

ELIANA (NCT02435849) was an international, multicentre, **phase II** trial which included paediatric and young adult patients (aged 3 years at screening to 21 at initial diagnosis) with r/r B-cell ALL (39). Data collected from ELIANA have been reported in the journal article by Laetsch *et al.* (2022) (36). This submission used the latest ELIANA data collected in November 2022 (42). By November 2022, 79 patients had received a tisagenlecleucel infusion (42).

ENSIGN (NCT02228096) was a US-based, phase II trial which similarly included paediatric and young adult patients (aged 3 years at screening to 21 at initial diagnosis)

with r/r B-cell ALL (40). Data collected from ENSIGN have been reported in the journal article by Maude *et al.* (2016) (43). This submission used the latest ENSIGN data collected in May 2019 (44). By May 2019, 64 patients had received a tisagenlecleucel infusion (44).

B2101J (NCT01626495) was the first tisagenlecleucel trial and was a US-based, **phase I/IIa** trial which included paediatric and young adult patients aged up to 24 years with **chemotherapy resistant** or refractory CD19+ B-cell leukaemia and **lymphoma (41)**. Data collected from B2101J have been reported in the journal article by Maude *et al.* (2014) (45). This submission used the latest B2101J data collected for patients with **non-CNS3** ALL (i.e. patients in which leukaemia had not spread to the **central nervous system**) in May 2018 (46). By May 2018, a total of 57 patients with non-CNS3 ALL had received a tisagenlecleucel infusion (46).

More information about the trials can be found here:

- ELIANA: (36); ClinicalTrials.gov: NCT02435849 (39).
- ENSIGN: Maude *et al.* 2016 (47); ClinicalTrials.gov: NCT02228096 (40).
- B2101J: Maude *et al.* 2014 (45); ClinicalTrials.gov: NCT01626495 (41).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

In the ELIANA, ENSIGN and B2101J studies, the efficacy of tisagenlecleucel was measured by the following outcomes (42, 44, 46):

Overall response rate

Overall response rate is the proportion of people who have achieved complete remission (i.e. there are no signs of ALL on scans or tests) following tisagenlecleucel infusion until the start of new cancer therapy such as allo-SCT (42, 44, 46). In ELIANA and ENSIGN, patients were assessed to have had achieved an overall response if the remission was maintained for at least 28 days (42, 44). Achieving a complete response is important for patients because they can expect their remission to last longer and are likely to live longer as a result.

In ELIANA, ENSIGN and B2101J, patients treated with tisagenlecleucel had high overall response rates (42, 44, 46). In the ELIANA trial, approximately 82% achieved an overall response. Results for this outcome are reported for the other trials in **Document B, Section B.2.6**.

Bone marrow MRD status

Bone marrow MRD status refers to the small number of cancer cells present in the bone marrow after treatment (48). Sensitive laboratory tests are used to determine MRD status, which can then be used to assess early treatment response and predict the likelihood of patients experiencing a relapse (49). An MRD of less than 0.01% is defined as “MRD-negative disease” (50). **MRD negativity** is associated with longer remissions and patients are likely to live longer as a result (49).

In ELIANA, ENSIGN and B2101J, a high percentage of patients who had achieved an overall response had also achieved bone marrow MRD negativity (42, 44, 46). In the ELIANA trial, 99% of patients who achieved an overall response were also MRD negative. Results for this outcome are reported for other trials in **Document B, Section B.2.6**.

Duration of response

Duration of response is the time between patients achieving complete remission and signs that ALL has started to grow again (i.e. the length of time before the patient experiences a relapse), or death due to ALL (42, 44, 46).

In ELIANA, ENSIGN and B2101J, a high percentage of patients were event-free at 6 months (42, 44, 46). In the ELIANA trial, patients recorded an average duration of 46.8 months before having signs that ALL has started to grow again (42). After achieving complete remission, the probability of patients in the ELIANA trial being event-free at 5 years was 49% (42). Results for this outcome are reported for other trials in **Document B, Section B.2.6**.

Event-free survival

Event-free survival is the time between tisagenlecleucel infusion and signs that ALL has started to grow again (i.e. the length of time before the disease starts to progress or a patient experiences a relapse), or death due to any cause following remission.

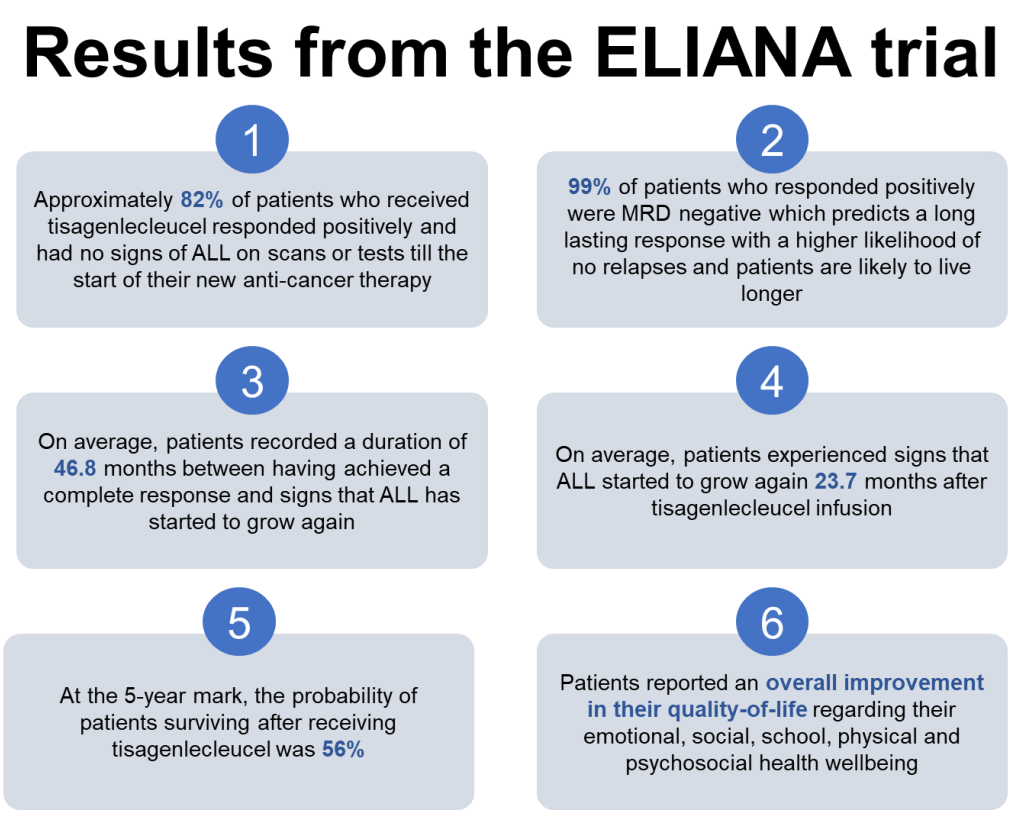
In ELIANA, ENSIGN and B2101J, a high percentage of patients were event-free at 6 months (42, 44, 46). In the ELIANA trial, the probability of patients being event-free 5 years after receiving tisagenlecleucel treatment was 42% (42). Results for this outcome are reported for other trials in **Document B, Section B.2.6**.

Overall survival

Overall survival is how long people live after receiving treatment (42, 44, 46). The long-term data collected from following up patients in the ELIANA trial showed that patients had long periods of remissions and were therefore likely to live longer (42). In the ELIANA trial, the probability of patients surviving for 5 years after receiving tisagenlecleucel was 56% (42). Results for this outcome are reported for other trials in **Document B, Section B.2.6**.

The key efficacy results from the ELIANA trial which represents the main source of evidence in this submission have been summarised below in **Figure 1.**

Figure 1: Key efficacy results for ELIANA



Abbreviations: ALL: acute lymphoblastic leukaemia; MRD: minimal residual disease.
Source: ELIANA CSR (17th Nov 2022) (42).

Indirect treatment comparison

Because trials for tisagenlecleucel are single-arm trials, no data are available directly comparing the effectiveness of tisagenlecleucel with that of other ALL treatment options. Therefore, an analysis called an **indirect comparison** was done to compare outcomes for tisagenlecleucel from ELIANA with outcomes for other ALL treatment options (blinatumomab and salvage chemotherapy) from other clinical trials (14, 15). This is a common approach in the evaluations of new medicines.

Statistical methods were used to adjust for any differences in patient characteristics that might impact on outcomes between patients in the ELIANA trial and the clinical trials investigating blinatumomab and salvage chemotherapy. This was to ensure the comparison of outcomes between tisagenlecleucel and existing treatments was as fair as possible, with differences in outcomes being due to the treatment received and not other factors. This statistical analysis is explained in further detail in **Document B, Section B.2.9**.

Overall, when compared to blinatumomab and salvage chemotherapy, the indirect comparison showed that patients who received tisagenlecleucel had a reduced risk of dying from the disease.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of tisagenlecleucel treatment

During the ELIANA study, patients were asked to answer questions about their quality of life, using various different questionnaires called PedsQL and EQ-5D for patients aged 8 years old and above (42). Patients reported an overall improvement in quality of life with regards to emotional, social, school, physical and psychosocial health wellbeing following tisagenlecleucel treatment (42). Results for this outcome are reported in detail in **Document B, Section B.2.6.2**.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own side effects and the same medicine can produce different reactions in different people. Tisagenlecleucel infusion is associated with side effects and all patients experienced at least one side effect. In ELIANA, ENSIGN and B2101J trials, side effects experienced by patients receiving tisagenlecleucel were generally manageable with supportive care provided (42, 44, 46). Side effects are most likely to happen in the first 8 weeks after the tisagenlecleucel infusion but can also develop later.

Evidence for the safety of tisagenlecleucel is based on a total of 200 patients with r/r B-cell ALL who have received tisagenlecleucel across all three clinical trials.

Very common side effects may affect more than 1 in 10 people. These include:

- High fever and chills. These may be symptoms of a serious condition called **cytokine release syndrome** (**CRS**) which may be life-threatening or fatal. Other symptoms of CRS are difficulty breathing, nausea, vomiting, diarrhoea, loss of

appetite, fatigue, muscle pain, joint pain, swelling, low blood pressure, fast heartbeat, headache, heart, lung and kidney failure and liver injury. These symptoms almost always occur within the first 14 days after infusion

- Problems such as altered thinking or decreased consciousness, loss of contact with reality, confusion, agitation, **seizures**, difficulty speaking and understanding speech, difficulty walking. These may be symptoms of a condition called **immune effector cell-associated neurotoxicity syndrome (ICANS)**
- Feeling warm, fever, chills or shivering, sore throat or mouth ulcers may be signs of an infection. Some infections may be life-threatening or fatal

These do not cover all of the possible side effects of tisagenlecleucel, just the most common. For other potential side effects, refer to the Patient Information Leaflet (Kymriah, INN-tisagenlecleucel (medicines.org.uk)) (38).

Managing side effects

The most common side effect experienced by patients was CRS (42, 44, 46). As a potentially life-threatening or fatal event, it is a key requirement for all tisagenlecleucel treatment centres to have access to necessary medication at hand to treat CRS (51). For example, the availability of **tocilizumab** to treat CRS must be verified before tisagenlecleucel infusion. Further information on the CRS management plan be found here (Kymriah, INN-tisagenlecleucel (europa.eu)) (51). Following tisagenlecleucel infusion, patients are monitored daily for the first 10 days and advised to remain in close proximity to qualified treatment facilities for at least 4 weeks, thereby ensuring prompt and effective management of any side effects (51).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

ALL accounts for a third of all childhood cancers yet there are limited treatment options that are licensed for use in this young population of people with ALL. While a high percentage of people with ALL respond positively to the initial chemotherapy treatment received, the leukaemia comes back (i.e. relapses) in 15% to 20% of them. For this group of people with ALL, their chances of responding positively to any further treatments decrease with every relapse. For people with ALL who have relapsed after receiving an allo-SCT or have had a second relapse, the licensed treatment options are extremely limited. This highlights the pressing need to license effective treatment options which can extend the life of people with ALL and also be potentially curative.

Tisagenlecleucel is already available for use via the CDF and represents an important treatment option for children and young adults with r/r B-cell ALL. The key benefits of tisagenlecleucel to patients with r/r B-cell ALL include that:

Tisagenlecleucel is potentially curative, providing the young population with ALL with the hope of cure.

Tisagenlecleucel is a one-time infusion, thereby reducing the number of clinical visits often associated with other treatment options for ALL.

As r/r B-cell ALL affects children and young adults, ALL and its treatment not only impacts the quality of life of people with ALL but also that of their parents/caregivers and support networks. Parents/caregivers and support networks often experience an increased financial burden and distress associated with caring for someone with ALL (19, 22, 23). Tisagenlecleucel as a treatment would hence reduce the impact felt by the extended network of people affected by a single ALL diagnosis.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

CAR T-cells are a novel immunotherapeutic approach to managing cancer with impressive efficacy. However, like all existing ALL treatments, tisagenlecleucel does not work for everyone and some patients might not respond to treatment. Furthermore, tisagenlecleucel treatment can have potentially life-threatening side effects such as CRS (51).

Tisagenlecleucel is therefore only given in specific hospitals under the supervision of healthcare professionals who are trained to administer and manage patients with tisagenlecleucel treatment (51). Specific drugs and equipment needed to manage side effects such as CRS are required to be available in hospitals before infusion (51).

All **systemic drug treatments** for r/r B-cell ALL are associated with side effects. Side effects associated with tisagenlecleucel treatment are usually manageable, and patients

would receive adequate supportive care by well-trained healthcare professionals following tisagenlecleucel infusion (42, 44, 46, 51).

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (tisagenlecleucel) with the existing treatment options (blinatumomab, salvage chemotherapy).

How the model reflects r/r B-cell ALL

The economic model was designed to reflect the key features of ALL and **clinical practice** in the UK. To do this, a model structure called a **partitioned survival model** was chosen, as this is used commonly to model cancer treatments. The model was used to predict future survival of patients with r/r B-cell ALL (based on survival equations) and compares tisagenlecleucel with other treatment options (blinatumomab and salvage chemotherapy).

Modelling how much tisagenlecleucel improves overall survival and event-free survival

The results of the ELIANA trial were used to inform the economic model as the ELIANA trial most closely resembles patients in clinical practice in the UK and had data with a long duration of **follow-up** (79.4 months) (42). The main results from the ELIANA trial that were used in the model were overall survival and event-free survival. These were the main

results used in the model because they were considered relevant to what would be considered a successful outcome when treating r/r B-cell ALL in clinical practice.

The results of the ELIANA trial only cover the study follow-up duration of 79.4 months, however the economic model simulates patients for the rest of their lifetime, a much longer period of time than the length of the trial. The model estimates that a proportion of patients who were to receive tisagenlecleucel are effectively "cured" and have survival that is similar to the general population.

Modelling how much tisagenlecleucel improves quality of life

The quality-of-life data that informed the model were from a study published by Kelly *et al.* (2015) on **cranial radiation therapy** in paediatric T-cell patients (52). This study converted quality-of-life measurements collected from questionnaires into **health utility inputs** to inform the economic model. The study by Kelly *et al.* (2015) represents the best source of quality-of-life data to inform the model given its long-term follow-up and large participant population (52).

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for the different r/r B-cell ALL treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in **Document B, Section 3.8.2.**

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section 3.10.3.**

Cost effectiveness results

In the model, tisagenlecleucel treatment was associated with higher costs, but also higher benefits (or '**quality-adjusted life years'** [**QALYs**]) than the other treatment options which include blinatumomab and salvage chemotherapy. This resulted in an **incremental cost-effectiveness ratio (ICER)** of £19,218 and £30,778 per QALY gained when compared to blinatumomab and salvage chemotherapy (FLAG-IDA). The ICER when compared with blinatumomab is below than the standard threshold that the NHS considers to be cost-effective (£30,000 per QALY gained) whilst it is above the threshold when compared with salvage chemotherapy (FLAG-IDA). However, as explained below, when the severity of r/r B-cell ALL is considered, the ICER falls below the threshold that the NHS considers to be cost-effective. However, it should be noted that these results are based on company-preferred assumptions and do not account for the confidential discount available for blinatumomab.

Benefits of tisagenlecleucel not captured in the economic analysis

A **decision modifier** for cancer drugs called the "end-of-life criteria" was previously used to assess the benefits of treatments for diseases associated with short **life expectancy**. If the "end-of-life" criteria was met (people with the disease were expected to live less than 24 months and treatment was anticipated to extend their life by more than 3 months), the NHS would consider treatments with higher costs (up to £50,000 per QALY gained) would be within the threshold considered cost-effective. However, a new decision modifier was introduced from 2022 onwards for all types of illnesses, called the severity modifier. The following text explains the impact of the severity modifier on the economic analysis for tisagenlecleucel.

Disease severity can be measured as the future health that would be lost by people with r/r B-cell ALL, compared with someone who does not have r/r B-cell ALL. Benefits measured in terms of QALYs are valued more highly for severe diseases, and when this **severity modifier** is applied, tisagenlecleucel was associated with an ICER of £11,304 and £18,105 per QALY gained when compared with blinatumomab and salvage chemotherapy (FLAG-IDA) respectively.

When considered in the context of a disease which affects a young population with extremely little chance of survival that reduces with each relapse, tisagenlecleucel treatment offers this population a potential for cure. Compared to other treatment options for r/r B-cell ALL, tisagenlecleucel is a one-time infusion and therefore, may improve patient experience by reducing the need for a number of clinical visits to receive multiple rounds of treatment.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Tisagenlecleucel is an innovative, one-time treatment, offering patients with limited treatment options the potential for cure.

r/r B-cell ALL is a condition that can have widespread impact on both the patients' and parents/caregivers' life with regards to mental and emotional wellbeing and quality of life. Tisagenlecleucel provides a potentially curative therapy for patients with limited treatment options. The impact of a cure is that it would reduce the burden on carers for patients with r/r ALL, and increase their quality of life. Moreover, tisagenlecleucel is a one-time treatment, in contrast to existing treatments which are administered regularly, which may be more convenient for patients. As a result, tisagenlecleucel has become an established treatment option, reducing the need for subsequent SCTs and potential associated toxicity.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Based on the Equality Act, age is a protected characteristic and therefore, highlights the legal duty of NICE to ensure services are provided to people regardless of age (53). People with ALL aged 26 years and above now have access to a CAR-T therapy via the CDF (TA893) (54). The decision to approve the routine funding of tisagenlecleucel would therefore ensure that people with ALL aged below 26 years have access to a CAR-T therapy option, independent of their age.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on ALL:

- Macmillan Cancer Support website: Acute lymphoblastic leukaemia (ALL) | Macmillan Cancer Support
- Leukaemia Care guide for patients with B-cell ALL: B-cell-Acute-Lymphoblastic-Leukaemia-ALL-Web-Version.pdf (leukaemiacare.org.uk)

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Acute lymphoblastic leukaemia (ALL)	A type of blood cancer that starts from white blood cells which normally help to fight infections in the body. In ALL,

	too many white blood cells are made and gather in the bone marrow
Allogenic stem cell transplant (allo-SCT)	A procedure in which healthy stem cells from a donor (sometimes a brother or sister, or a person unrelated who has similar stem cells) are collected from the blood or bone marrow before treatment, stored, and then given to the patient after treatment. People with ALL may receive high doses of chemotherapy which kills the leukaemia cells as well as the healthy cells in the bone marrow. A stem cell transplant then replaces the stem cells that were destroyed with healthy stems cells.
Anaemia	A condition where there is reduced number of red blood cells and can cause symptoms such as tiredness, weakness or shortness of breath.
Anaesthetic	A drug that cause partial or complete loss of feeling for a period of time.
Antigen	Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances that come from outside the body. Body tissues and cells, including cancer cells, also have antigens on them that can cause an immune response.
Antihistamine	A type of medicine used to control symptoms of allergies. Allergies refer to reactions by the body's immune system and could be in response to foreign substances in the body.
B-cell	A type of white blood cell in the immune system that helps to fight infections.
Blinatumomab	A type of targeted cancer drug called a monoclonal antibody which attaches to targets in the body such as antigens on the surface of cancer cells.

Biopsy	The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue.
Bone marrow	This is a soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made.
Cancer Drugs Fund (CDF)	A funding source used for cancer drugs in England that show good results in trials but do not have enough data to be approved for routine use in NHS hospitals. The availability of tisagenlecleucel via the CDF allows more data to be collected on how well the drug works.
Central nervous system (CNS)	The central nervous system is part of the nervous system and consists of the brain and spinal cord. The main function of the CNS is to control the body's functions which includes how one thinks, feels, moves, learns and remembers.
Chimeric Antigen Receptor-T (CAR-T)	CAR-T cell therapy is a type of immunotherapy whereby patients' own immune cells are collected and are then modified to recognise and bind to specific proteins found on the surface of cancer cells. Once bound to the specific proteins, the CAR-T cells can then attack and kill cancer cells.
Chemotherapy	A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein.
Chemotherapy resistant	This refers to cancer cells being unaffected by chemotherapy treatment and therefore cannot be killed and cleared from a patient's body.
Clinical practice	This refers to the treatments commonly offered to patients, often guided by clinical guidelines that provide recommendations on the use of different treatments.
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new

	methods of screening, prevention, diagnosis or treatment of a disease.
Complete blood count	A comprehensive type of blood test which measures different substances present in blood, including white blood cells, red blood cells and platelets.
Complete remission	The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured.
Control treatment	This refers to the treatment given to the control group in clinical studies. The control group does not receive the experimental treatment which refers to the treatment that the study investigators are interested to find out more about.
Cranial radiation therapy	A type of radiation therapy that is targeted to the brain. Radiation therapy refers to use of intense energy beams (also known as radiation) to kill cancer cells.
Cyclophosphamide	A type of chemotherapy drug which slows down or stops the growth of cancer cells by damaging their DNA. DNA stands for deoxyribonucleic acid which make up genes that carry important information required for cells to make functional proteins.
Cytokine release syndrome (CRS)	A set of symptoms that can develop as a side effect of CAR T-cell treatment or as a response to infection. CRS is a type of aggressive immune system reaction which may be life-threatening or fatal. Symptoms of CRS include difficulty breathing, nausea, vomiting, diarrhoea, loss of appetite, fatigue, muscle pain, joint pain, swelling, low blood pressure, fast heartbeat, headache, heart, lung and kidney failure and liver injury. These symptoms almost always occur within the first 10 days after infusion.
Diphenhydramine	A type of antihistamine medicine which controls symptoms of allergies. Allergies refer to reactions by the body's immune system and could be in response to foreign substances in the body.

Decision modifier	This refers to factors which have not been included in the calculation of improvement in quality of life, but are important factors that would influence the decision-making to recommend treatments. Such decision modifiers include the “end-of-life criteria” which results in the greater value being placed on treatments for patients with short life expectancies.
Donor	An individual, sometimes a brother or sister, from whom blood, tissue or organs are taken by healthcare professionals to either transfuse or transplant into a patient.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
European Medicines Agency	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
Febrile neutropenia	This refers to the development of fever in patients with neutropenia. Neutropenia refers to a low number of neutrophils, a type of white blood cell, which are required to fight infections. Febrile neutropenia is a common but serious complication of cancer treatment.
Fludarabine	A type of chemotherapy drug that stops cells from making and repairing DNA. DNA stands for deoxyribonucleic acid which make up genes that carry important information required for cells to make functional proteins. By preventing DNA from being made or repaired, this drug stops the growth and multiplication of cancer cells.
Follow-up	The period of time that participants in a trial are followed up to monitor their health after they have received a treatment in a study.
Genetic abnormality	This refers to alterations in the genetic material and can be passed down from parents to children. Genetic abnormalities may also randomly occur in a person resulting in change in the genetic material. Some genetic

	abnormalities may result in diseases and affect one's health while others do not.
Genetically modified	This refers to the alteration of genetic material, usually performed in a controlled environment such as a laboratory. Genes carry important information required for cells to make functional proteins.
Haemoglobin	A protein found in red blood cells which carries and transports oxygen to different parts of the body.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial.
Health utility inputs	A measure of the preference or value that an individual or society gives a particular health state. This is generally a number between 0 (representing death) and 1 (representing perfect health).
Hypotension	Low blood pressure.
Immune effector cell-associated neurotoxicity syndrome (ICANS)	A set of symptoms that may be experienced by people receiving certain types of immunotherapy. Symptoms of ICANS include altered thinking or decreased consciousness, loss of contact with reality, confusion, agitation, seizures, difficulty speaking and understanding speech, difficulty walking.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Immune system	The immune system defends the body from infection. It is made up of different organs, cells, and proteins that work together.
Immune cells	Cells from the immune system.
Indirect comparison	A type of comparison done in evaluation of new medicines to compare the outcomes of treatments studied in different

	clinical trials. This type of comparison is indirect as the treatments were studied in different trials.
Inotuzumab ozogamicin	A type of targeted cancer drug called a monoclonal antibody which attaches to targets in the body such as antigens on the surface of cancer cells.
Intravenously	A type of method to inject drugs through the veins.
Leukaemia	A cancer of blood cells.
Leukapheresis	Removal of the blood to collect specific blood cells. The remaining blood is returned to the body.
Life expectancy	Number of years a person is expected to live.
Lymph node	A small bean-shaped structure that is part of the body's immune system. Lymph nodes filter substances that travel through the lymphatic fluid, and they contain lymphocytes that help the body fight infection and disease. There are hundreds of lymph nodes found throughout the body. They are connected to one another by lymph vessels. Clusters of lymph nodes are found in the neck, axilla (underarm), chest, abdomen, and groin. For example, there are about 20–40 lymph nodes in the axilla. Also called lymph gland.
Lymphoblast	An immature or developing form of white blood cell. Lymphoblasts grow into a mature form known as lymphocytes.
Lymphocyte	A type of white blood cell that is essential in the immune system. The three major types of lymphocyte are T-cells, B-cells and natural killer (NK) cells, which have specific roles in the immune system.
Lymphodepleting chemotherapy	This involves giving patients a short course of chemotherapy to decrease the number of T-cells in the patient's body. This then makes room for the new CAR T-cells to grow once infused.

Lymphoma	A cancer of the lymphatic system which is part of the body's immune system and protects the body from infections and diseases.
Maintenance chemotherapy	Treatment that is given to help keep cancer from coming back after it has been eliminated following the initial treatment.
Minimal residual disease (MRD)	This refers to a scenario where there are only a small number of cancer cells left in the patient's body after receiving cancer treatment.
Monoclonal antibody	A type of protein that is made in the laboratory and can bind to certain targets in the body, such as antigens, on the surface of cancer cells.
MRD negativity	When patients have an MRD level of less than 0.01%, they are classified as having MRD negativity.
Non-CNS3	CNS3 status indicates the involvement of the central nervous system (CNS) in the disease. Non-CNS3 therefore refers to the lack of involvement of the CNS.
Open-label	A type of clinical trial where participants know what treatment they receive.
Paediatric	This refers to people aged less than 18 years and for simplicity is used interchangeably in this document with the term "children".
Paracetamol	A commonly used medicine to treat pain and fevers.
Partitioned survival model	A type of economic model commonly used to map the life of cancer patients. The model predicts the probability of patients staying in pre-specified states of health over a specific time period.
Peripheral blood smear	A test to examine levels of red blood cells, white blood cells and platelets.

Phase I	Clinical trials which are testing new treatments are usually into different stages, also known as phases, based on the characteristics and aims of the trial. Phase I refers to an early phase of the trial which involves a small group of participants. The main aim of a phase I trial is to find out more about the treatment and its side effects.
Phase II	A clinical trial phase which involves a larger number of participants compared to a phase I trial. The main aim of a phase II trial is to check how much of the drug should be given, find out more about the side effects and how well the treatment works.
Phase IIA	A phase II trial can sometimes be further divided into phase IIa and phase IIb. In a phase IIa trial, the main aim of the trial is to check how much of the drug should be given to participants.
Phase IIB	In a phase IIb trial, the main aim of the trial is to study how well the drug works at the doses given to participants.
Philadelphia (Ph) chromosome	A specific genetic abnormality present in leukaemia cancer cells.
Platelet	A tiny, disc-shaped cell that is found in the blood and spleen. They help form blood clots to slow or stop bleeding and help wounds heal.
Post-transplant	The period after receiving allo-SCT transplant.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Quality-adjusted life year (QALY)	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale, where 0 represents death and 1 represents perfect health). It is often measured in terms of the

	person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out daily activities.
Refractory	A disease or condition that does not respond to treatment.
Relapse	The return of a disease or the signs and symptoms of a disease after a period of improvement.
Remission	This refers to the disease responding to treatment where signs of cancer have disappeared.
Salvage chemotherapy	Chemotherapy treatment given after the disease has not responded to prior treatment or has come back.
Seizures	A sudden, uncontrolled burst of electrical activity that happens in the brain. This results in temporary changes in muscle movement, awareness or behaviour.
Severity modifier	A method used to place an increased value in the improvement in quality of life, measured by QALYs, in people with severe diseases. In more severe diseases, these QALY measurements would be further multiplied by a value of either 1.2 or 1.7.
Side effect	A side effect is a medical problem which doctors think is probably caused by the treatment in the trial.
Single-arm	In a single-arm trial, everyone who is enrolled in the trial receives the same treatment that is being investigated in the study.
Spleen	A fist-sized organ that is an important part of the immune system which acts like a blood filter.

Stem cell	A type of cell which can develop into different types of blood cells, including red blood cells, white blood cells, blood-clotting cells (platelets)
Systemic drug treatment	Treatment that affects the body as a whole or that acts specifically on systems that involve the entire body, such as the cardiovascular, respiratory, gastrointestinal, or nervous systems.
T-cell	A another type of white blood cell which helps the body fight infections.
Targeted cancer drug	A type of cancer treatment which works by finding and attacking cancer cells specifically.
Tisagenlecleucel	A type of CAR T-cell therapy which contains genetically modified white blood cells that targets the CD19 antigen which is found on the surface of cancerous B-cells in B-cell ALL.
Tocilizumab	A drug that suppresses immune system response and can be used to control side effects experienced by patients receiving cancer treatment.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. European Medicines Agency. Kymriah (tisagenlecleucel). An overview of kymriah and why it is authorised in the EU. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah [Last accessed: 14 April 2023].

2. National Institute for Health and Care Excellence. TA554: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. Available at: https://www.nice.org.uk/guidance/TA554. [Last accessed: 4 May 2023].

3. Children with Cancer UK. Acute Lymphoblastic Leukaemia. Available at: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/acute-lymphoblastic-leukaemia/ [Last accessed: 4 May 2023].

4. American Cancer Society. How is Childhood Leukemia Classified? Available at: . https://www.cancer.org/cancer/leukemia-in-children/detection-diagnosis-staging/how-classified.html [Last accessed: 4 May 2023].

5. Leukemia and Lymphoma Society. Ph-positive ALL Therapy. Available at: https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment/ph-positive-all-therapy [Last accessed: 4 May 2023].

6. American Cancer Society. Signs and Symptoms of Acute Lymphocytic Leukemia (ALL). Available at: https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html#:~:text=If%20ALL%20spreads%20to%20the,fluid%20buildup%20and%20trouble%20breathing. [Last accessed: 4 August 2023].

7. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence by sex and UK country. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero [Last accessed: 4 May 2023].

8. Leukemia & Lymphoma Society. Relapsed and refractory. Available at: https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment/relapsed-and-refractory#:~:text=In%20these%20cases%2C%20the%20disease,or%20%E2%80%9Crelapsed%20ALL%E2%80%9D). [Last accessed: 4 August 2023].

9. Nguyen K, Devidas M, Cheng S-C, La M, Raetz EA, Carroll WL, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22(12):2142-50.

10. Pui C-H, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol. 2015;33(27):2938-48.

11. Nebraska Hematology-Oncology (NHO). Refractory ALL. Available at: http://yourcancercare.com/types-of-cancer/leukemia/childhood-acute-lymphoblastic-leukemia/childhood-acute-lymphoblastic-leukemia-refractory [Last accessed: 4 May 2023].

12. Dana-Farber Cancer Institute. Relapsed Childhood Acute Lymphoblastic Leukemia. Available at: https://www.dana-farber.org/relapsed-childhood-acute-lymphoblastic-leukemia/#:~:text=Relapsed%20acute%20lymphoblastic%20leukemia%2C%20or,will%20have%20the%20disease%20return. [Last accessed: 14 April 2023].

13. Ko RH, Ji L, Barnette P, Bostrom B, Hutchinson R, Raetz E, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2009;28(4):648-54.

14. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, et al. Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381-9.

15. Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol. 2006;24(12):1917-23.

16. Brown AL, Sok P, Taylor O, Woodhouse JP, Bernhardt MB, Raghubar KP, et al. Cerebrospinal Fluid Metabolomic Profiles Associated With Fatigue During Treatment for Pediatric Acute Lymphoblastic Leukemia. J Pain Symptom Manage. 2021;661(3):464-73.

17. Leukemia & Lymphoma Society. Cancer-related fatigue. Available at: https://www.lls.org/treatment/managing-side-effects/cancer-related-fatigue. [Last accessed: 9 August 2023].

18. Steur LMH, Kaspers GJL, van Someren EJW, van Eijkelenburg NKA, van der Sluis IM, Dors N, et al. The impact of maintenance therapy on sleep-wake rhythms and cancer-related fatigue in pediatric acute lymphoblastic leukemia. Support Care Cancer. 2020;28(12):5983-93.

19. Sherief LM, Kamal NM, Abdalrahman HM, Youssef DM, Alhady MAA, Ali AS, et al. Psychological impact of chemotherapy for childhood acute lymphoblastic leukemia on patients and uheir parents. Medicine (Baltimore). 2015;94(51):e2280.

20. Kizilocak H, Okcu F. Late Effects of Therapy in Childhood Acute Lymphoblastic Leukemia Survivors. Turk J Haematol. 2019;36(1):1-11.

21. Essig S, von der Weid NX, Strippoli MP, Rebholz CE, Michel G, Rueegg CS, et al. Health-related quality of life in long-term survivors of relapsed childhood acute lymphoblastic leukemia. PLoS One. 2012;7(5):e38015.

22. Pagano E, Baldi I, Mosso ML, di Montezemolo LC, Fagioli F, Pastore G, et al. The economic burden of caregiving on families of children and adolescents with cancer: A population-based assessment. Pediatr Blood Cancer. 2014;61(6):1088-93.

23. Ren Y, Li X. Direct and indirect costs of families with a child with acute lymphoblastic leukaemia in an academic hospital in China: a cross-sectional survey. BMJ Open. 2019;9(7):e030511.

24. Leukemia Care. B-cell Acute Lymphoblastic Leukaemia (ALL). Available at: https://media.leukaemiacare.org.uk/wp-content/uploads/B-cell-Acute-Lymphoblastic-Leukaemia-ALL-Web-Version.pdf. [Last accessed: 4 August 2023].

25. Canadian Cancer Society. Staging acute lymphoblastic leukemia. Available at: https://cancer.ca/en/cancer-information/cancer-types/acute-lymphoblastic-leukemia-all/staging#:~:text=Cancers%20that%20form%20solid%20tumours,has%20no%20standard%20staging%20system. [Last accessed: 4 August 2023].

26. Children's Cancer and Leukaemia Group. Clinical treatment guidelines. Available at: https://www.cclg.org.uk/what-we-do/clinical-treatment-guidelines [Last accessed: 4 May 2023].

27. Children's Cancer and Leukaemia Group. UK Acute Lymphoblastic Leukaemia (UKALL) 2019 Interim Guidelines. Available at: https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/UKALL_2019_Interim_Guidance_Final.pdf [Last accessed: 4 May 2023]. 2019.

28. Cancer Research UK. Treatment for ALL that has not gone away with treatment or has come back. Available at: https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/treatment/relapsed-refractory. [Last accessed: 8 August 2023].

29. Leukemia & Lymphoma Society. Allogenic stem cell transplantation. Available at: https://www.lls.org/treatment/types-treatment/stem-cell-transplantation/allogeneic-stem-cell-transplantation. [Last accessed: 9 August 2023].

30. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2018.

31. Pan-London Blood Cancer. Pan-London Haemato-Oncology Clinical Guidelines. Acute Leukaemias and Myeloid Neoplasms. Part 1: Acute Lymphoblastic Leukaemia. Available at: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-ALL-Guidelines-Jan-2020.pdf [Last accessed: 4 May 2023]. 2020.

32. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010;376(9757):2009-17.

33. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2023.

34. Leukemia & Lymphoma Society. Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts. Available at: https://www.lls.org/sites/default/files/file_assets/longtermlateeffectschildhood.pdf. [Last accessed: 4 August 2023].

35. Mody R, Li S, Dover DC, Sallan S, Leisenring W, Oeffinger KC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. 2008;111(12):5515-23.

36. Laetsch TW, Maude SL, Rives S, Hiramatsu H, Bittencourt H, Bader P, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. J Clin Oncol. 2022;41(9):1664-9.

37. Cancer Research UK. CAR T-cell therapy. Available at: https://about-cancer.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy. [Last accessed: 4 August 2023].

38. Medicines. Patient Information Leaflet. Available at: https://www.medicines.org.uk/emc/files/pil.9456.pdf. [Last accessed: 4 August 2023].

39. ClinicalTrials.gov. ELIANA (NCT02435849). Available at: https://clinicaltrials.gov/ct2/show/NCT02435849 [Last accessed: 1 May 2023].

40. ClinicalTrials.gov. ENSIGN (NCT02228096). Available at: https://clinicaltrials.gov/ct2/show/NCT02228096 [Last accessed: 1 May 2023].

41. ClinicalTrials.gov. B2101J (NCT01626495). Available at: https://clinicaltrials.gov/ct2/show/NCT01626495?term=PEDI-CART&rank=1 [Last accessed: 1 May 2023].

42. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (17th November 2022 data cut-off). Data on File. 2023.

43. Maude SL, Pulsipher MA, Boyer MW, Grupp SA, Davies SM, Phillips CL, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis. Am Soc Hematology.; 2016.

44. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter study to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (24th May 2019 data cut-off). Data on File. 2019.

45. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England journal of medicine. 2014;371(16):1507-17.

46. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Subjects with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (7th May 2018 data cut-off). Data on File. 2019.

47. Maude SL, Barrett DM, Rheingold SR, Aplenc R, Teachey DT, Callahan C, et al. Efficacy of humanized CD19-targeted chimeric antigen receptor (CAR)-modified T cells in children and young adults with relapsed/refractory acute lymphoblastic leukemia. Am Soc Hematology; 2016.

48. Leukemia & Lymphoma Society. Minimal Residual Disease (MRD). Available at: https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS35_MRD_Final_2019.pdf. [Last accessed: 4 August 2023].

49. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010(1):7-12.

50. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia (Trial Protocol). The New England journal of medicine. 2018;378(5):439-48.

51. European Medicines Agency. Kymriah (tisagenlecleucel). Summary of Product Characteristics (SmPC). Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf [Last accessed: 14 April 2023].

52. Kelly MJ, Pauker SG, Parsons SK. Using nonrandomized studies to inform complex clinical decisions: the thorny issue of cranial radiation therapy for T-cell acute lymphoblastic leukemia. Pediatric blood & cancer. 2015;62(5):790-7.

53. National Institute for Health and Care Excellence. NICE's equality objectives and equality programme 2020 - 2024. Available at: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.nice.org.uk%2FMedia%2FDefault%2FAbout%2FWho-we-are%2FPolicies-and-procedures%2FEquality%2520objectives%2520and%2520equality%2520programme%25202020%2520-%25202024.docx&wdOrigin=BROWSELINK [Last accessed: 8 August 2023]. 2021.

54. National Institute for Health and Care Excellence. TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. Available at: https://www.nice.org.uk/guidance/ta893. [Last accessed: 21 June 2023].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]

Clarification questions

November 2023

File name	Version	Contains confidential information	Date
ID6290 Tisagenlecleucel clarification letter	V0.2	No	15/11/2023

Section A: Clarification on search strategy

A1. Company's submission (CS) Appendices, Section D1.1, Tables 4 and 5, pages 11-12. Why were the 2019 searches of MEDLINE and Embase limited to English and German language material only? Whilst this limit did not apply to the 2023 searches, these had a cut-off of 2019, meaning that the limit effectively still applies to earlier results.

The limit to English language and German material was applied within the original systematic literature review (SLR) to reduce the number of potential hits returned from the database searches. This limit was removed in the most recent SLR update as it was judged that the impact on the number of results returned was marginal and otherwise redundant as only English-language articles were eligible for inclusion in the SLR. On this basis it was also deemed that there would be limited value in rerunning the database searches prior to 2019, given the low likelihood that relevant data would have been missed. It is also important to note that the searches undertaken by the Company in TA554 were considered to be appropriate by the external assessment group (EAG).[1]

A2. CS Appendices, Section D1.1, page 8. It is stated that *"for the March 2023 SLR update alone, the bibliographies of all relevant SLRs and (N)MAs identified during the SLR were hand-searched to identify any additional, relevant studies for Inclusion."* If SLRs and NMAs were intended to be used for this purpose, why were they not included in the study filters used for the searches of MEDLINE and EMBASE?

Whilst a bespoke filter for SLRs/network meta-analyses (NMAs) could have been used (such as those developed by the Scottish Intercollegiate Guidelines Network [SIGN] or McMaster University) within the database searches, the titles and/or abstracts of relevant SLRs/NMAs routinely report on the study type(s) they are aggregating, whether they are randomised controlled trials (RCTs), interventional studies or observational studies; as such, these SLRs/NMAs would be identified using the broad text word search terms employed in the study design filters for primary data. The inclusion of a bespoke SLR/NMA filter was therefore judged to be unnecessary.

Section B: Clarification on clinical effectiveness data

Patient pathway and comparators

B1. CS, Section B.1.3.2, page 29. The text states that inotuzumab ozogamicin is only indicated for CD22+ disease. Please state what proportion of the target population for tisagenlecleucel have CD22+ ALL and of these how many of these patients were aged ≥18 years.

The underlying mechanism of action of tisagenlecleucel involves preferentially targeting the cluster of differentiation 19 (CD19) antigen, a glycoprotein with near-universal expression on B-cell precursors and B-cells.[2] Inotuzumab ozogamicin targets cluster of differentiation 22 (CD22), a different member of the B-cell antigen family with tissue distribution of 60-90%.[3]

Whilst the licence for tisagenlecleucel includes patients aged up to 25 years, it is predominantly used in paediatric patients as reflected by the mean age of 12 years in the principal trial (ELIANA) informing the CS;[4] this is similar to the median age of 13 years reported in the National Health Service England (NHSE) Cancer Drugs Fund (CDF) report.[5] Given clinical experts have confirmed that the ELIANA trial is generalisable to UK clinical practice and since 17.7% of patients in the ELIANA trial were ≥ 18 years old, the estimated proportion of these patients with CD22+ acute lymphoblastic leukaemia (ALL) is 10.6%–15.9% (i.e. 17.7% of 60–90%).[4, 6] CD22 expression was not a measured characteristic in the ELIANA trial, however the proportion of patients with CD22 expression is not anticipated to differ from published values.

As mentioned in Section B.1.3.2 of the CS, the target population for tisagenlecleucel is "paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse", in line with its licensed EMA marketing authorisation.[7] Inotuzumab on the other hand is licensed for adult patients (i.e. ≥ 18 years old) with CD22+ r/r B-cell ALL and is more commonly used earlier in the treatment pathway at first relapse, which does not form part of the licence for tisagenlecleucel or the target population in the CS.[8] To a lesser extent, inotuzumab ozogamicin is used to treat primary refractory patients, as an eventual bridge to allogenic stem cell transplant (allo-SCT) or tisagenlecleucel, as per clinical expert feedback received as part of this appraisal.[6] However, this forms only a small proportion of the patient population of relevance to this submission (7.6% and 9% of patients had primary refractory disease in ELIANA and the NHSE CDF report, respectively). [4, 5] As such, only a small overlap in patient population is expected to exist between patients considered for treatment with tisagenlecleucel and inotuzumab in UK clinical practice, irrespective of CD22 expression.

B2. Priority. CS, Section B.1.3.2, page 27. The text states that *"The only curative approach to the treatment of relapse is allo-SCT, and thus the aim of treatment in this setting remains the achievement of a CR, which is a prerequisite for allo-SCT.*"

Does the company consider it possible to achieve cure without subsequent allo-SCT consolidation therapy:

a) following tisagenlecleucel?

b) following blinatumomab?

c) following salvage chemotherapy?

If yes, why was allo-SCT considered clinically necessary in the three tisagenlecleucel studies?

The Company considers it possible to achieve cure without allo-SCT following tisagenlecleucel but not possible to achieve cure following blinatumomab and salvage chemotherapy (FLAG-IDA [fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin]), without subsequent allo-SCT consolidation therapy. As detailed in Section B.1.2 of the CS, tisagenlecleucel acts as a "living drug" by using patients' own T-cells and their capacity for memory and surveillance, thereby providing a durable response, potentially over the course of a lifetime. In contrast, the aim of treatment with blinatumomab and salvage chemotherapy remains to achieve complete remission (CR) so that patients may proceed onto consolidation with allo-SCT.

Consolidation with allo-SCT remains the only treatment option to achieve long-term, durable response following treatment with blinatumomab or FLAG-IDA. UK ALL interim guidelines explicitly note the consideration of consolidation treatment with allo-SCT (if eligible) in the context of treatment with blinatumomab or NOPHO blocks (confirmed as being equivalent to FLAG-IDA by clinical experts).[9] No such mention of SCT is made in the context of treatment with tisagenlecleucel.

Clinical expert feedback received as part of this appraisal further confirmed that blinatumomab and salvage chemotherapy are offered with the aim of achieving CR to bridge to curative allo-SCT.[6] However, as detailed in Section B.3.2.3 of the CS, page 125, comparison of clinician estimates of the subsequent allo-SCT rates following blinatumomab, salvage chemotherapy and tisagenlecleucel are limited and would need to be interpreted with caution given the strict eligibility criteria for patients to be in CR following blinatumomab and salvage chemotherapy to permit allo-SCT. Therefore, patients selected for treatment with comparator therapies are likely to have a higher probability of achieving CR and proceeding to allo-SCT. Comparing the subsequent allo-SCT rates based on efficacy data sources would therefore be more appropriate and represent fair comparisons between tisagenlecleucel and comparators.[6]

The objective of bridging to allo-SCT is confirmed by data from the respective data sources used to inform the efficacy of each treatment: in von Stackelberg *et al*. (2016), of the 27 patients who achieved CR, 24 (88.9%) received subsequent SCT; in Jeha *et al.* (2006), 38.9% of patients who achieved CR received subsequent SCT, with ineligibility for allo-SCT presumably preventing the remaining 61.11% of responders from receiving allo-SCT.[10, 11] In contrast, the curative intent of tisagenlecleucel treatment is demonstrated by low subsequent SCT rates of 22.78% recorded in the ELIANA trial (DCO; 17th Nov 2022), of which 83% had received subsequent allo-SCT whilst in remission (amounting up to 19% of all patients in the trial), for reasons elaborated on below.[4] The curative potential of tisagenlecleucel is further corroborated by even lower subsequent SCT

rates recorded in the NHSE CDF report wherein 12.28% of patients (14/114) received a subsequent SCT after tisagenlecleucel.[5]

The trials for CAR-T were initiated over 5 years ago and this was a revolutionary innovation with no prior analogues to inform appropriate treatment course of action. In the US, some physicians had previously chosen to consolidate with allo-SCT therapy following tisagenlecleucel. Whilst no data were collected, the reasons for consolidation may have been varied, such as relapse following response, clinician judgement based on disease status (MRD positivity, B-cell recovery), or concerned parents wanting their children to receive a known curative treatment option. However, consolidation with allo-SCT therapy following tisagenlecleucel is no longer considered an appropriate treatment course of action for patients in remission as confirmed by UK clinical experts and NHSE data collection for tisagenlecleucel use in real-world practice.[5, 6]

As outlined in Section B.2.12 of the CS, the long-term follow-up data from the latest data cut-off (DCO; 17th Nov 2022) of the ELIANA trial (79.4 months median follow-up from tisagenlecleucel infusion) provides robust evidence on the curative potential of tisagenlecleucel, demonstrated by durable remissions and prolonged overall survival (OS) observed.[4] UK clinical experts consulted as part of this appraisal with experience in the treatment of relapsed/refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL) and the use of tisagenlecleucel have stated that tisagenlecleucel is given with curative intent in UK clinical practice.[6] Experts also agreed that the overall survival (OS) extrapolations, generated using mixture-cure models based on ELIANA data, were reflective of UK clinical practice.[6]

Nevertheless, it is important to note that the economic analysis includes SCT rates that are aligned to the most relevant efficacy data source in the model, with an additional scenario analysis presented for tisagenlecleucel informed by the latest real-world evidence (RWE) for tisagenlecleucel in NHS practice.

Tisagenlecleucel clinical evidence

B3. CS, Section B.2.6, page 54 to 104. Please confirm that all time-to-event data on EFS and OS presented in the CS reflect the latest available data cut-off (DCO) for each study (ELIANA DCO 17th Nov 2022, ENSIGN DCO 24th May 2019, B2101J DCO 7th May 2018). Are subsequent data cuts expected for any of these three tisagenlecleucel studies?

Yes, it can be confirmed that all time-to-event data on event-free survival (EFS) and OS presented in the CS reflect the latest available data cut-off (DCO) for each study (ELIANA DCO 17th Nov 2022, ENSIGN DCO 24th May 2019, B2101J DCO 7th May 2018).[4, 12, 13] As mentioned in Section B.2.11 of the CS, no subsequent data cuts are expected for any of the three tisagenlecleucel studies.

B4. CS, Section B.1.2, Table 3, page 22. The text states that the recommended lymphodepleting chemotherapy regimen prior to tisagenlecleucel consists of fludarabine, cyclophosphamide, cytarabine and etoposide. However, both CS Section B.2.3.3 (Table 5) and CS Section B.3.2.3 state that lymphodepleting

chemotherapy consists of fludarabine and cyclophosphamide. Please clarify why there are differences between these sections.

The recommended lymphodepleting chemotherapy is aligned to Section B.1.2, Table 3 and the Summary of Product Characteristics (SmPC) for tisagenlecleucel.[14] The recommended lymphodepleting chemotherapy regimen is as follows:

- Fludarabine (30 mg/m^2 intravenous [IV] daily for 4 days) and cyclophosphamide (500 mg/m^2 IV daily for 2 days starting with the first dose of fludarabine)
- **OR** cytarabine (500 mg/m^2 IV daily for 2 days) and etoposide (150 mg/m^2 IV daily for 3 days starting with the first dose of cytarabine) *if the patient has experienced a previous grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemo-refractory state to a cyclophosphamide containing regimen administered shortly before lymphodepleting chemotherapy*

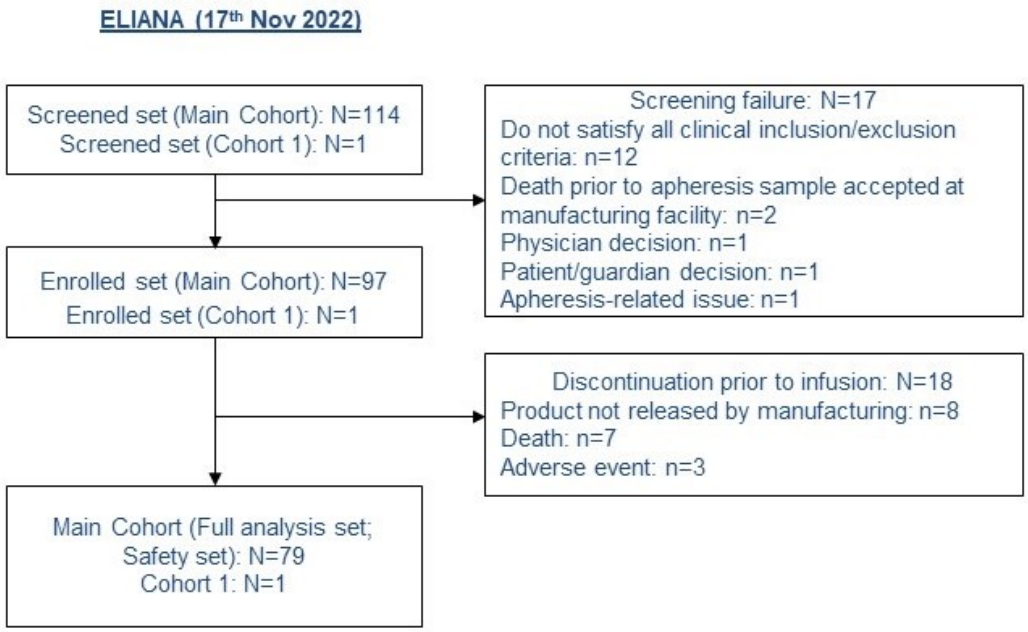
The text in Section B.2.3.3 (Table 5) and Section B.3.2.3 of the CS erroneously omitted mention of cytarabine and etoposide for certain patients with prior adverse reactions to cyclophosphamide. The Company can confirm that the recommended lymphodepleting chemotherapy regimens and their respective costs were both accounted for correctly in the economic model: 98.61% of patients modelled to receive lymphodepleting chemotherapy were assumed to receive the first regimen (fludarabine and cyclophosphamide), and 1.39% of patients were assumed to receive the second regimen (cytarabine and etoposide).

B5. CS, Section B.2.3. Please provide a CONSORT flow diagram for the full ITT population for each study.

For those patients who were screened but not enrolled in the ENSIGN, ELIANA and B2101J trials, please provide an overview of the reasons why patients were not enrolled.

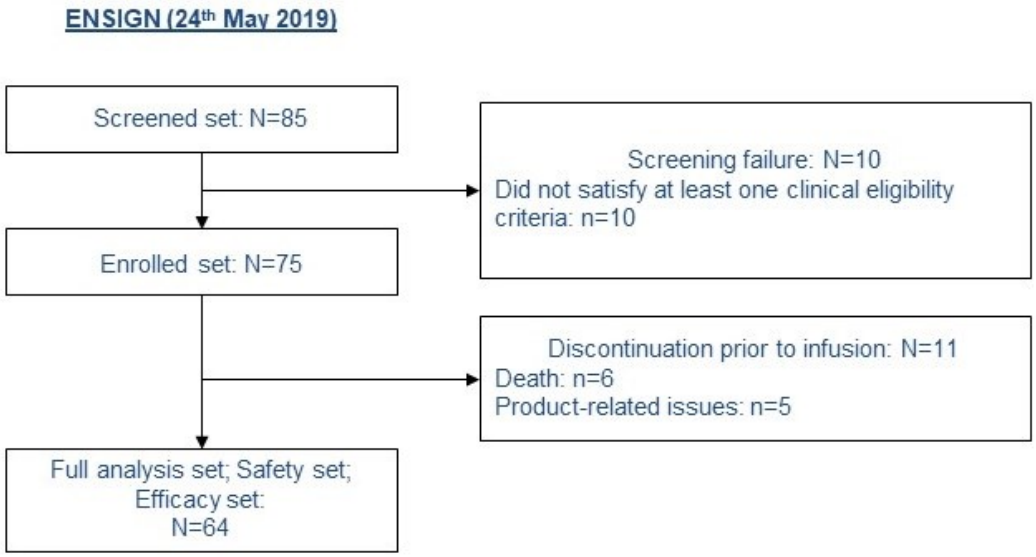
The CONSORT flow diagrams for the full intention-to-treat (ITT) populations for ELIANA, ENSIGN and B2101J are presented below in Figure 1, Figure 2 and Figure 3 respectively.

Figure 1: CONSORT diagram of patient flow (ELIANA)



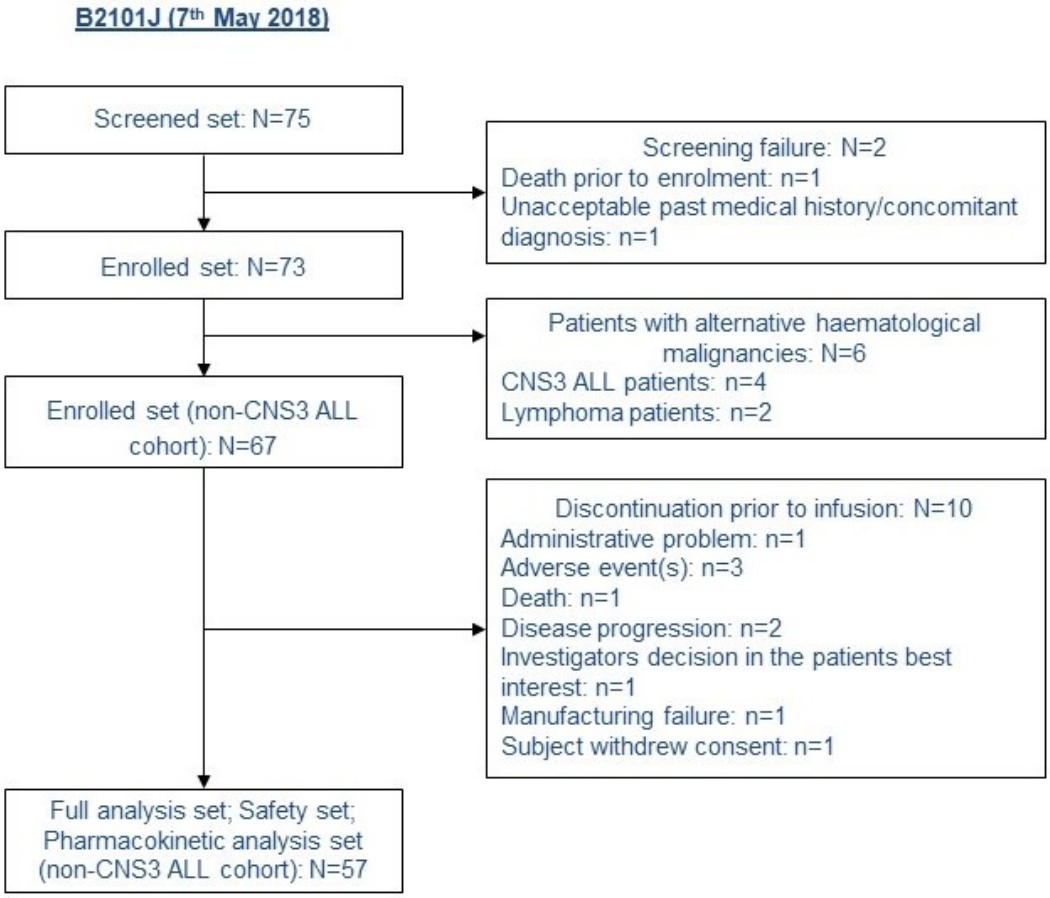
Source: ELIANA CSR (17th Nov 2022).[4]

Figure 2: CONSORT diagram of patient flow (ENSIGN)



Source: ENSIGN CSR (24th May 2019).[12]

Figure 3: CONSORT diagram of patient flow (B2101J)



Source: B2101J CSR (7th May 2018).[13]

B6. CS, Section B.2.3.2, Table 5, page 39. The table states the locations of sites included in the tisagenlecleucel studies. For ELIANA, please state how many centres, and how many included patients, were from the US, EU, Japan, and specifically from the UK.

The countries of sites included in the ELIANA trial are presented in Table 1 below.

Table 1: Patients enrolled and infused in countries of sites included in the ELIANA trial

Country	Total Enrolled (n)	Total Infused (n)
Australia	1	1
Austria	2	2
Belgium	4	3
Canada	7	6
Germany	6	4
Spain	9	8
France	6	6
Italy	1	1
Japan	8	6
Norway	4	4
US	50	39
Grand Total	**98**	**80**

Note: The latest DCO for ELIANA included an additional Cohort 1, intended to include patients who were at very high risk at first relapse. One patient was recruited in Cohort 1 before enrolment was terminated early. This patient was not included in the main cohort results reported in the CS, but is included in the above data for patients enrolled and infused.
Abbreviations: CS: company submission; DCO: data cut-off; US: United States.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022).[15]

B7. CS, Section B.2.3.2, Table 5, 39. The table describes the intra-patient dose escalation of tisagenlecleucel in Study B2101J. This is also discussed in Section B.2.8 of the CS.

(a) Please state how many patients received each of one, two or three infusions.

The number of patients that received one, two or three infusions in B2101J is presented below.

Table 2: Tisagenlecleucel infusions in B2101J

Total number of infusions	N (%)
1	13 (22.8)
2	25 (43.9)
3	16 (28.1)
>3	3 (5.3)

Abbreviations: CSR: clinical study report.
Source: B2101J CSR (7th May 2018).[13]

(b) Please state the number of days (e.g., median, min, max) over which the multiple infusions were administered.

The number of days over which the multiple infusions were administered are presented below in Table 3.

Table 3: Number of days over which multiple infusions were administered

Number of days over which multiple infusions were administered	B2101J (safety set) (N=57)[a]
n	**44[b]**
Median	49
Min–Max	1–651

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only
[b]44 patients received multiple infusions in B2101J.
Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system.
Source: Novartis Data on File (2023; B2101J DCO: 7th May 2018).[15]

(c) Please provide the median (and min/max) dose received in B2101J, ENSIGN and ELIANA.

The median dose and median weight-adjusted dose received by patients in each trial are reported in Table 4 below, along with their respective ranges.

Table 4: Doses received in ELIANA, ENSIGN and B2101J

Characteristic	ELIANA (safety analysis set) (N=79)	ENSIGN (full analysis set) (N=64)	B2101J (full analysis set) (N=57)[a]
Tisagenlecleucel dose received (10^8 cells)			
Median	1.00	1.15	3.30
Min–Max	0.03–2.60	0.09–2.50	0.10–11.40
Tisagenlecleucel weight-adjusted dose received (10^6 cells/kg)			
Median	3.00	3.40	7.50
Min–Max	0.20–5.40	0.20–5.00	0.60–22.60

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
Abbreviations: CNS: central nervous system; CSR: clinical study report.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN CSR (24th May 2019);[12] B2101J CSR (7th May 2018).[13]

(d) Does the company believe that this dose escalation approach would have impacted on clinical outcomes?

B2101J was a single centre, phase I/IIa, open-label study to assess the safety, tolerability and engraftment potential of tisagenlecleucel, and therefore, used a dose escalation approach. Patients in ELIANA, ENSIGN and in UK RWE, as per the NHSE CDF report, received single infusions.

As reported in Section B.2.6 of the CS, high overall response rates (ORR) were reported across all three tisagenlecleucel trials at 82.3%, 70.3% and 94.7% for ELIANA, ENSIGN and B2101J respectively. All three tisagenlecleucel trials and UK RWE showed comparable OS with UK RWE reporting more favourable OS results than the ELIANA

and ENSIGN trials, presented below, suggesting that the dose escalation approach in B2101J would not have impacted clinical outcomes.

Table 5: Summary of OS results in ELIANA, ENSIGN, B2101J and UK RWE

OS	ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)	UK RWE (N=121)
% at 6 months (95% CI)	88.6 (79.3, 93.9)	84.4 (72.9, 91.3)	86.0 (73.9, 92.7)	90.0 (82.0, 94.0)
% at 12 months (95% CI)	77.1 (66.1, 84.9)	65.4 (52.4, 75.7)	78.9 (65.9, 87.5)	81.0 (73.0, 88.0)
% at 24 months (95% CI)	67.8 (56.1, 77.0)	54.7 (39.8, 67.4)	64.9 (51.1, 75.7)	72.0 (62.0, 80.0)
% at 30 months (95% CI)	65.0 (53.2, 74.5)	48.6 (31.2, 64.0)	61.4 (47.5, 72.6)	NR
% at 60 months (95% CI)	55.7 (43.6, 66.3)	N/A	46.5 (30.8, 60.8)	NR
Median (months) (95% CI)	NE (45.6, NE)	29.9 (15.1, 42.4)	47.7 (28.3, NE)	NE

Abbreviations: CI: confidence interval; NE: Not estimable; NHSE: National Health Service England; NR: Not reported; OS: overall survival; RWE: real-world evidence; UK: United Kingdom.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018);[13] NHSE CDF Report.[5]

B8. CS, Section B.2.3.3, page 47 to 49. Please provide, if available, the baseline characteristics for the ITT population (i.e., including patients who did not receive infusion) from the latest data cut of the ENSIGN, ELIANA and B2101J trials.

The baseline characteristics for the ITT population (i.e. including patients who did not receive infusion) are not available for the latest data cuts of the tisagenlecleucel trials.

B9. CS, Section B.2.3.3, page 47 to 49. Please provide the number of patients, if any, with Philadelphia chromosome positive (Ph+ve) disease in the ENSIGN, ELIANA and B2101J trials.

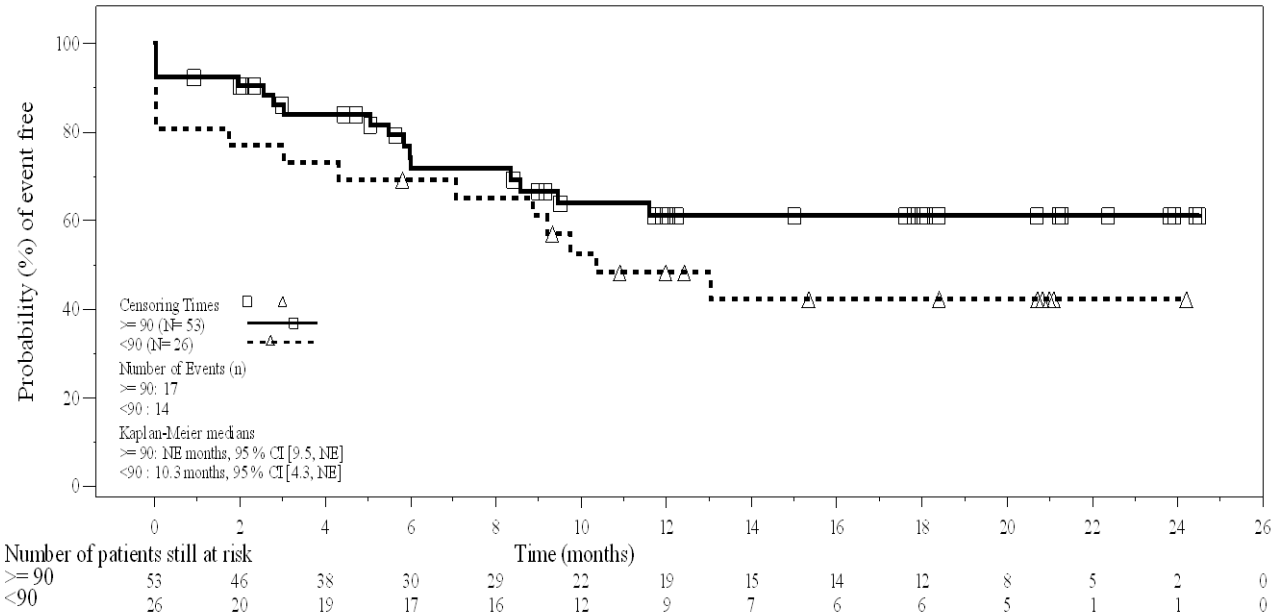
As of the latest data cut-offs for the respective trials, the number of patients with Philadelphia chromosome positive (Ph+ve) disease was as follows:

- ELIANA (DCO; 31st Dec 2017): 2/79 (2.5%)[4]
- ENSIGN (DCO; 24th May 2019): 2/64 (3.1%)[12]
- B2101J (DCO; 7th May 2018): 3/57 (5.3%)[13]

B10. CS, Section B.2.3.3, Table 7, page 47 to 49. The text states that there were differences in performance status between three tisagenlecleucel studies. Whilst it is true that there are differences in the percentage with a score of 100, the studies were similar in the percentage with a score over 80 (84%, 92%, 93%) and with a score over 70 (94%, 95%, 98%). Please comment on whether these differences are likely to have substantially affected trial outcomes.

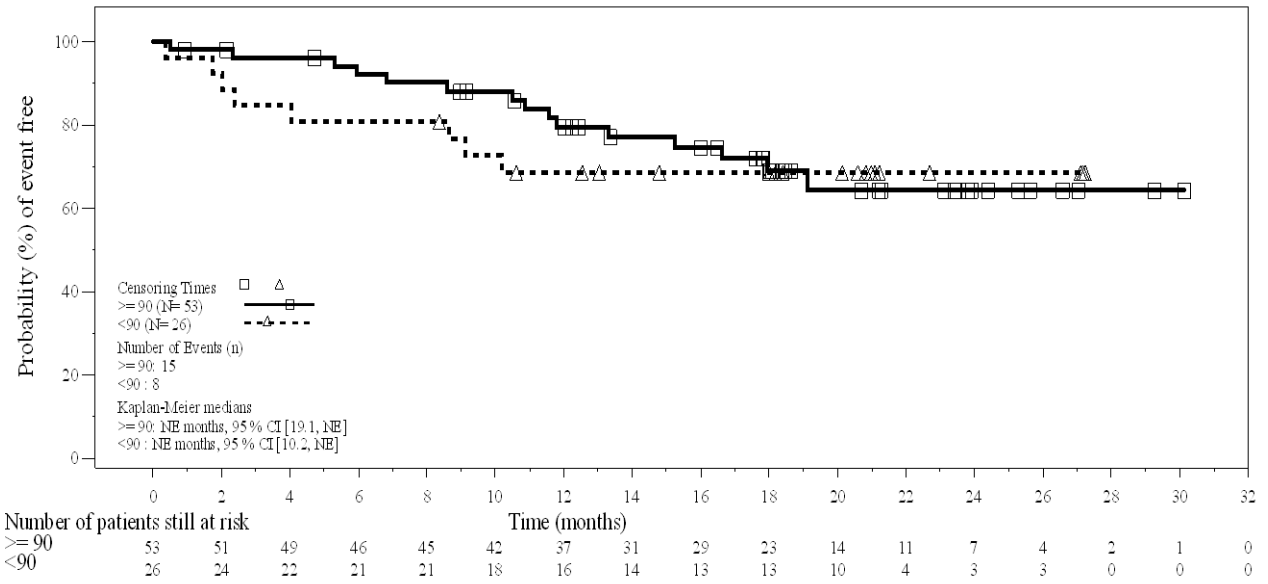
As noted by the EAG, the differences in performance status referenced in the CS relate primarily to those patients with performance scores of ≥90, which were slightly higher in B2101J (84.2%), than in ELIANA or ENSIGN (67.1% and 71.9%).[4, 12, 13] Performance status was noted by clinician advice to the EAG in the original submission as a possible prognostic factor.[16] However, as shown in Figure 4 and Figure 5 below, previously conducted subgroup analyses from the ELIANA trial (DCO; 31st December 2017) show only limited separation in EFS and OS survival curves in patients with performance status above and below 90.[15] The relatively small differences between trials in the percentages of patients with performance scores of ≥90 are therefore unlikely to have materially impacted long term trial outcomes.

Figure 4: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by baseline Karnofsky/Lansky performance status (≥90 vs <90) by IRC assessment in ELIANA



Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: Novartis Data on File (2023; ELIANA DCO: 31st Dec 2017).[15]

Figure 5: Kaplan-Meier curve for OS (without censoring for allo-SCT) by baseline Karnofsky/Lansky performance status (≥90 vs <90) by IRC assessment in ELIANA



Abbreviations: CI: confidence interval; IRC: independent review committee; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: Novartis Data on File (2023; ELIANA DCO: 31st Dec 2017).[15]

B11. CS, Section B.2.3.3, Table 7, pages 47 to 49.

Please clarify the difference between “chemo-refractory” and “relapsed disease”.

“Chemo-refractory” was defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukaemia and “relapsed disease” was defined as second or greater bone marrow relapse or any bone marrow relapse after allo-SCT and ≥ 6 months from allo-SCT at the time of tisagenlecleucel infusion.

Please present data per study on the percentage of patients who were: (i) primary refractory, (ii) refractory to later lines of therapy, (iii) relapsed post-SCT, (iv) relapsed post other treatments. Please also break down these data by whether patients had first, second, third relapse etc.

The percentage of primary refractory patients in each trial is reported in Table 7 of the CS; further breakdown of disease status based on prior therapy received is not available.

B12. CS, Section B.3.2.2, page 113. Please provide details of the descriptive statistics median (range), mean (SD) on the average time from enrolment to infusion in the ELIANA, ENSIGN, and B2101J studies.

The time from enrolment to tisagenlecleucel infusion for ELIANA and ENSIGN and B2101J studies is presented in Table 6 below. These data were not available for the latest DCO (7th May 2018) of the B2101J trial; the data from the 30th January 2017 DCO have been presented instead.

Table 6: Summary of time (in days) from enrolment to tisagenlecleucel infusion

	ELIANA	ENSIGN	B2101J
n	80	64	56
Mean (SD)	50.4 (17.95)	42.4 (18.59)	67.5 (38.39)
Median	45.5	37.5	59.0
Min-Max	26–105	22.0–117.0	14–167

Abbreviations: SD: standard deviation.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 30th Jan 2017.[15]

B13. CS, Section B.3.2.2, page 113. The CS states *"…ongoing process improvements in tisagenlecleucel manufacturing have reduced the throughput time, thereby resulting in increased manufacturing capacity and an increased proportion of patients receiving tisagenlecleucel in clinical practice."* Please provide further information about the current proportion of patients for whom tisagenlecleucel is planned and successfully infused, and the time from ordering to infusion in UK clinical practice.

The manufacturing time in UK clinical practice for tisagenlecleucel is 3 weeks.

In terms of successful infusions, as stated in the NHSE CDF report, a total of 160 applications (unique patients) were planned between 16th November 2018 and 30th June 2023 wherein a total of 136 successful tisagenlecleucel infusions were performed in UK clinical practice.[5] The total number of successful tisagenlecleucel infusions include a total of 15 patients in devolved administrations (Scotland, Wales or Northern Irelands) which were not included in the main analyses presented in the NHSE CDF report.[5]

B14. Priority. CS, Section B.2.6.1, Table 12, page 54. Please provide a revised version of CS Table 12 including the following information:

- EFS: For all three tisagenlecleucel studies and the pooled dataset, please include the % event-free at 24 months and 30 months for all studies (as presented in the text in subsequent sections)
- EFS: For all three tisagenlecleucel studies and the pooled dataset, please include the number and % experiencing an EFS event at the latest cut-off (as presented in the text in subsequent sections).
- For ENSIGN, the text in Section B.2.6.3 presents EFS data for treatment failure and relapse but does not appear to include deaths (28/64, 43.8%). Please provide this figure for all EFS events including deaths, and include in Table 12 as requested above.

- OS: For all three tisagenlecleucel studies and the pooled dataset, please include the % alive at 24 months and 30 months for all studies (as presented in the text in subsequent sections).

A revised version of Table 12 in the CS with the additional requested information on EFS and OS is presented below in Table 7.

As per Section B.2.6.3 of the CS, EFS in the ENSIGN trial was defined as the time from the date of first tisagenlecleucel infusion to the **earliest** date of either death due to any cause after remission, relapse, or treatment failure, as determined by independent review committee (IRC) assessment.[12] The Company therefore confirms that the EFS data reported for ENSIGN has taken into consideration all EFS events, including deaths, as per the EFS definition. There were no deaths recorded as EFS events in the ENSIGN trial and the data presented (28/64, 43.8%) therefore accurately reflects the total number of EFS events recorded in ENSIGN.[12]

Table 7: Revised table for summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J

n (%)	ELIANA (N=79)[a]	ENSIGN (N=64)	B2101J (N=57)[b]	Pooled dataset (N=200)
Primary efficacy results				
BOR[c]				
ORR (CR+CRi) (95% CI; p value)	65 (82.3%) (72.1, 90.0; NR)	45 (70.3%) (57.6, 81.1; <0.0001*)	54 (94.7%) (85.4,98.9)	N/A
CR	49 (62.0%)	38 (59.4%)	42 (73.7%)	N/A
CRi	16 (20.3%)	7 (10.9%)	12 (21.1%)	N/A
NR	7 (8.9%)	13 (20.3%)	3 (5.3%)	N/A
Unknown[d]	7 (8.9%)	6 (9.4%)	0	N/A
ORR with bone marrow MRD negative (i.e. MRD <0.01%) (95% CI)	64 (81.0%) (70.6, 89.0)	43 (67.2%) (54.3, 78.4)	49 (86.0%) (74.2, 93.7)	N/A
n (%)	**ELIANA (N=79)**	**ENSIGN (N=64)**	**B2101J (N=57)[b]**	**Pooled dataset (N=200)**
Secondary efficacy results				
DoR (/RFS)				
% event free at 6 months (95% CI)	80.8 (68.0, 88.9)	79.5 (62.9, 89.3)	73.6 (58.7, 83.8)	N/A
% event free at 12 months (95% CI)	67.4 (53.2, 78.1)	70.5 (52.8, 82.6)	61.0 (45.0, 73.6)	N/A
% event free at 60 months (95% CI)	49.2 (34.6, 62.3)	N/A	44.9 (29.4, 59.3)	N/A
Median (months) (95% CI)	46.8 (17.8, NE)	NE (13.6, NE)	27.9 (8.0, NE)	N/A
EFS				
% event free at 6 months (95% CI)	71.7 (59.8, 80.6)	67.0 (53.5, 77.4)	74.3 (60.4, 83.9)	71.9 (65.7, 78.6)

% event free at 12 months (95% CI)	57.2 (44.5, 68.0)	53.6 (39.3, 66.0)	57.8 (42.4, 70.4)	56.0 (48.9, 64.1)
% event free at 24 months (95% CI)	49.6 (36.7, 61.2)	47.8 (33.0, 61.1)	50.2 (34.9, 63.7)	48.6 (41.3, 57.3)
% event free at 30 months (95% CI)	47.7 (34.8, 59.4)	47.8 (33.0, 61.1)	45.2 (30.2, 59.0)	45.7 (38.2, 54.6)
% event free at 60 months (95% CI)	41.8 (29.1, 53.9)	N/A	42.5 (27.7, 56.6)	41.0 (33.3, 50.4)
Median (months) (95% CI)	23.7 (9.2, NE)	15.6 (6.4, NE)	24.9 (8.6, NE)	20.9 (11.6,NE)
Number of events (%)	38/79 (48.1)	28/64 (43.8)	27/57 (47.4)	93/200 (46.5)
OS				
% at 6 months (95% CI)	88.6 (79.3, 93.9)	84.4 (72.9, 91.3)	86.0 (73.9, 92.7)	86.5 (81.9, 91.4)
% at 12 months (95% CI)	77.1 (66.1, 84.9)	65.4 (52.4, 75.7)	78.9 (65.9, 87.5)	73.9 (68.1, 80.3)
% at 24 months (95% CI)	67.8 (56.1, 77.0)	54.7 (39.8, 67.4)	64.9 (51.1, 75.7)	63.2 (56.6, 70.4)
% at 30 months (95% CI)	65.0 (53.2, 74.5)	48.6 (31.2, 64.0)	61.4 (47.5, 72.6)	59.8 (53.1, 67.4)
% at 60 months (95% CI)	55.7 (43.6, 66.3)	N/A	46.5 (30.8, 60.8)	47.3 (39.8, 56.3)
Median (months) (95% CI)	NE (45.6, NE)	29.9 (15.1, 42.4)	47.7 (28.3, NE)	47.7 (36.8, NE)
Number of deaths (%)	33/79 (41.8)	30/64 (46.9)	27/57 (47.4)	90/200 (45.0)

[a]Primary endpoint analysis was not repeated in ELIANA CSR (17th Nov 2022);[4] data for ELIANA primary efficacy presented refer to interim analysis performed in the ELIANA CSR (13th Apr 2018)[17] and presented in Grupp *et al.* 2019.[18]
[b]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[c]BOR is reported within 3 months, 6 months and 28 days of tisagenlecleucel respectively for ELIANA, ENSIGN and B2101J, respectively.
[d]'Unknown' is assigned in case the Baseline assessment of the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame.
*No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: CR with incomplete blood count recovery; DOR: duration of remission; FAS: full analysis set; MRD: minimum residual disease; NE: not estimable; NR: not reported; ORR: overall remission rate
Source: ELIANA CSR (13th Apr 2018);[17] ELIANA CSR (17th Nov 2022);[4] ENSIGN CSR (24th May 2019);[12] B2101J CSR (7th May 2018);[13] Grupp *et al.* (2019);[18] Laetsch *et al.* (2023).[19]; Grupp *et al.* (2018).[20]

B15. Priority. CS, Figures 9, 13, 16 and 20, pages 61, 69, 73 and 79. The EFS Kaplan-Meier plots in Figure 20 do not appear to match the individual EFS plots for ELIANA (Figure 9), ENSIGN (Figure 13) or B2101J (Figure 16). Please clarify which of the plots include censoring for allo-SCT, and whether the differences between the plots are due to this or another reason. Please provide alternative versions of each of these plots with and without censoring for allo-SCT.

All Kaplan-Meier plots referred to within this question include censoring for allo-SCT; however, Figure 20 from the CS considers deaths which occur after haematopoietic stem cell transplant (HSCT) or treatment other than HSCT (patients otherwise censored in the EFS analysis), whilst

Figure 9, Figure 13 and Figure 16 of the CS (all taken from the CSRs) censor for HSCT regardless of later deaths.

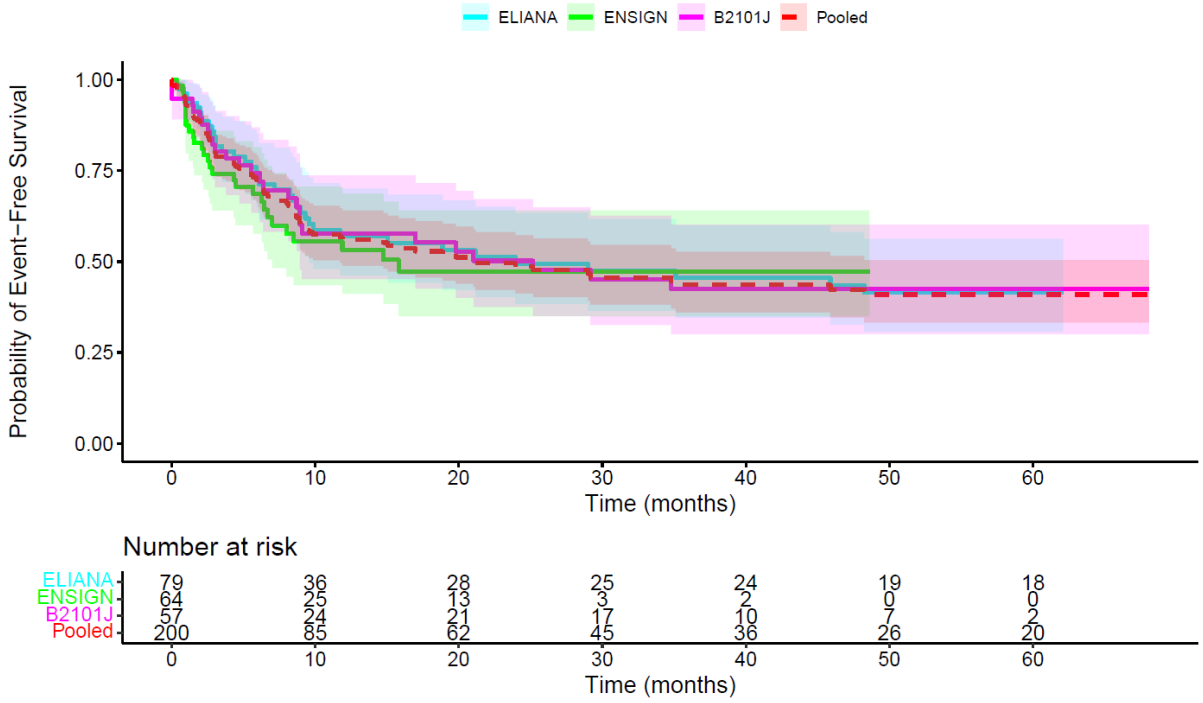
This led to a small discrepancy between the EFS data presented in the CSRs and the EFS data used in the pooled analysis. To ensure that these are aligned, the Company have updated the pooled analysis with the EFS reported in the CSR for consistency.

Accordingly, the EFS data used to inform the economic model have been updated to include censoring for HSCT regardless of later deaths. In addition, a discrepancy in patient numbers has been corrected; the Company apologises for this error, and has updated the economic model (both for ELIANA and the pooled data incorporated as per the response to D2).

There is a limited difference in Kaplan–Meier results (the difference is primarily driven by changes to the ENSIGN and B2101J data, where the difference in the number of events is 6 and 5, respectively, whilst for ELIANA, there is a difference of 4).[12, 13, 21] Results for the updated company base case are reported in the Appendix, which demonstrate a limited impact on results.

An updated plot for Figure 20 of the CS is presented below. In the pooled analysis, median EFS is 20.9 months (95% CI: 11.6, NA) and 93 of the 200 patients infused with tisagenlecleucel (46.5%) had experienced an EFS event (death due to any cause after remission, relapse, or treatment failure). The probability of being event-free was 56.0% (95% CI: 48.9%, 64.1%) at one year, 48.6% (95% CI: 41.3%, 57.3%) at two years, 43.6% (95% CI: 36.1%, 52.7%) at three years, 41.0% (95% CI: 33.3%, 50.4%) at four years and 41.0% (95% CI: 33.3%, 50.4%) at five years.

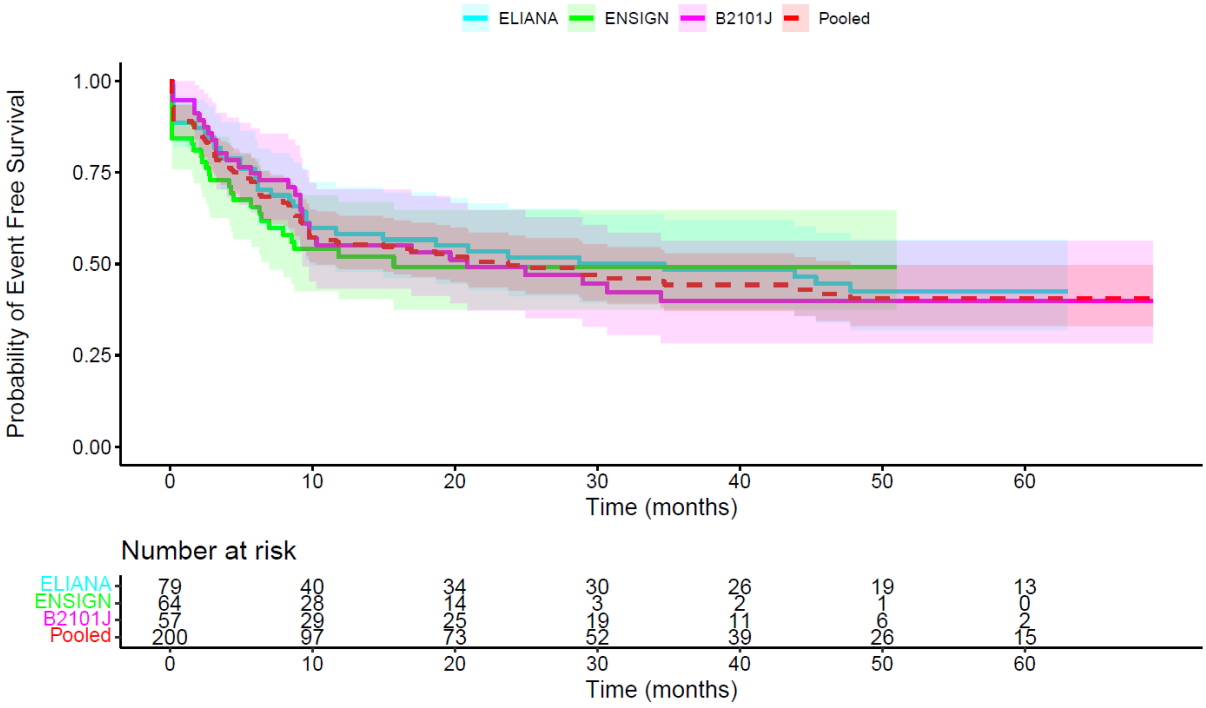
Figure 6: Updated EFS Kaplan-Meier plot with censoring for allo-SCT (for Figure 20 from CS)



Abbreviations: allo-SCT: allogenic stem cell transplantation; CS: Company submission; EFS: event-free survival.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018).[13]

The Kaplan-Meier plot for EFS without censoring for allo-SCT is presented in Figure 7. Kaplan-Meier data for EFS and OS is provided in the reference pack for Question D1.

Figure 7: Kaplan-Meier plot for EFS without censoring for allo-SCT



Abbreviations: allo-SCT: allogeneic stem cell transplantation; EFS: event-free survival.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018).[13]

B16. Priority. CS, Section B.2.6, page 54. With respect to each of ELIANA, ENSIGN and B2101J, and for the pooled dataset, please provide the following information for patients who did not receive tisagenlecleucel infusion:

(a) The number and proportion of non-infused patients who received leukapheresis

(b) The number and proportion of non-infused patients who received bridging chemotherapy

(c) The number and proportion of non-infused patients who received lymphodepleting chemotherapy.

The proportion of non-infused patients who received leukapheresis, bridging chemotherapy, and lymphodepleting chemotherapy in each of the three tisagenlecleucel trials, and the pooled analysis, are shown in Table 8 below.

Table 8: Proportion of patients receiving pre-infusion treatments in ELIANA, ENSIGN and B2101J, and pooled data sets

	ELIANA		ENSIGN		B2101J		Pooled	
	Infused N=79 n (%)	Not infused N=18 n (%)	Infused N=64 n (%)	Not infused N=11 n (%)	Infused N=57 n (%)	Not infused N=10 n (%)	Infused N=200 n (%)	Not infused N=39 n (%)
Number of patients who received leukapheresis	79 (100)	18 (100)	64 (100)	11 (100)	57 (100)	10 (100)	200 (100)	39 (100)
Number of patients who received bridging chemotherapy	69 (87.3)	13 (72.2)	57 (89.1)	9 (81.8)	5 (8.8)	1 (10.0)	131 (65.5)	23 (59.0)
Number of patients who received lymphodepleting chemotherapy	76 (96.2)	1 (5.6)	60 (93.8)	1 (9.1)	53 (93.0)	0	189 (94.5)	2 (5.1)

Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019; B2101J DCO: 7th May 2018).[15]

B17. CS, Section B.2.6.2, page 64. PROs in ELIANA (PedsQL and EQ VAS) are only provided for patients who achieved CR/Cri following tisagenlecleucel infusion.

Please clarify why data are presented for this subgroup only.

Whilst the paediatric quality of life questionnaire (PedsQL) and EuroQoL-visual analogue scales (EQ-VAS) data are available from the full analysis set of patients in ELIANA, the majority of patients for whom post baseline patient-reported outcome (PRO) results were available were patients with CR or complete remission with incomplete blood recovery (CRi) (n=44/52 at Baseline) as patients who did not respond to tisagenlecleucel mostly discontinued from the study.[21] As mentioned in Section B.2.6.2 of the CS, in patients ≥8 years old who achieved CR/CRi following tisagenlecleucel infusion, the mean change from Baseline in EQ-VAS was 16.9 at Month 6 (n=36), 20.5 at Month 12 (n=24), 22.4 at Month 24 (n=20), and 23.6 at Month 60 (n=15).[21] This is comparable to the mean change from Baseline in EQ-VAS observed in the overall population of patients ≥8 years old (i.e. not restricted to patients who have achieved CR/CRi following tisagenlecleucel infusion): 16.6 at Month 6 (n=37), 20.5 at Month 12 (n=24), 22.4 at Month 24 (n=20), and 23.6 at Month 60 (n=15).[15]

The Company notes that Section B.2.6.2, page 63 of the CS reads: “In the full analysis set (data cut-off 17th Nov 2022), the mean change from Baseline in the PedsQL total score was 14.8 at Month 6, 23.8 at Month 12, 26.2 at Month 24 and 25.3 at Month 60, indicating an overall improvement in HRQoL after tisagenlecleucel infusion”. However, these data were for the patient population who had achieved CR/CRi and therefore, this should read as “In patients ≥8 years old *who achieved CR/CRi*, the mean change from Baseline in the PedsQL total score was 14.8 at Month 6 (n=37), 23.8 at Month 12 (n=23), 26.2 at Month 24 (n=20) and 25.3 at Month 60 (n=14), indicating an overall improvement in HRQoL after tisagenlecleucel infusion.”[21] This remains comparable to the mean change from Baseline in PedsQL observed in the overall population of patients ≥8 years old (i.e. not restricted to patients who achieved CR/CRi following tisagenlecleucel infusion): 14.7 at Month 6 (n=38), 23.8 at Month 12 (n=23), 26.2 at Month 24 (n=20), and 25.3 at Month 60 (n=14).[15]

Please also provide EQ-5D-3L results based on the questionnaire.

The European quality of life 5-Dimensions 3-Levels (EQ-5D-3L) results based on the questionnaire for the full population in ELIANA, not restricted to patients who have achieved CR/CRi, are presented in Table 11 below.

Table 9: EQ-5D-3L at Baseline through Month 60 in ELIANA (FAS)

Timepoint EQ-5D dimension	All patients (N=61)				
	Total n	No problems n (%)	Some problems n (%)	Severe problems n (%)	Missing n (%)
Baseline					
Mobility	61	20 (32.8)	28 (45.9)	4 (6.6)	9 (14.8)
Self-care	61	34 (55.7)	15 (24.6)	3 (4.9)	9 (14.8)
Usual activities	61	20 (32.8)	22 (36.1)	9 (14.8)	10 (16.4)
Pain/discomfort	61	18 (29.5)	28 (45.9)	6 (9.8)	9 (14.8)

Anxiety/depression	61	29 (47.5)	22 (36.1)	1 (1.6)	9 (14.8)
Month 3					
Mobility	61	30 (49.2)	12 (19.7)	0 (0.0)	19 (31.1)
Self-care	61	36 (59.0)	6 (9.8)	0 (0.0)	19 (31.1)
Usual activities	61	29 (47.5)	12 (19.7)	1 (1.6)	19 (31.1)
Pain/discomfort	61	26 (42.6)	16 (26.2)	0 (0.0)	19 (31.1)
Anxiety/depression	61	26 (42.6)	16 (26.2)	0 (0.0)	19 (31.1)
Month 6					
Mobility	61	25 (41.0)	13 (21.3)	1 (1.6)	22 (36.1)
Self-care	61	33 (54.1)	5 (8.2)	1 (1.6)	22 (36.1)
Usual activities	61	24 (39.3)	14 (23.0)	1 (1.6)	22 (36.1)
Pain/discomfort	61	25 (41.0)	14 (23.0)	0 (0.0)	22 (36.1)
Anxiety/depression	61	31 (50.8)	7 (11.5)	1 (1.6)	22 (36.1)
Month 12					
Mobility	61	18 (29.5)	7 (11.5)	0 (0.0)	36 (59.0)
Self-care	61	20 (32.8)	4 (6.6)	1 (1.6)	36 (59.0)
Usual activities	61	17 (27.9)	7 (11.5)	1 (1.6)	36 (59.0)
Pain/discomfort	61	18 (29.5)	7 (11.5)	0 (0.0)	36 (59.0)
Anxiety/depression	61	21 (34.4)	4 (6.6)	0 (0.0)	36 (59.0)
Month 24					
Mobility	61	18 (29.5)	3 (4.9)	0 (0.0)	40 (65.6)
Self-care	61	20 (32.8)	1 (1.6)	0 (0.0)	40 (65.6)
Usual activities	61	19 (31.1)	2 (3.3)	0 (0.0)	40 (65.6)
Pain/discomfort	61	17 (27.9)	4 (6.6)	0 (0.0)	40 (65.6)
Anxiety/depression	61	17 (27.9)	4 (6.6)	0 (0.0)	40 (65.6)
Month 60					
Mobility	61	15 (24.6)	1 (1.6)	0 (0.0)	45 (73.8)
Self-care	61	16 (26.2)	0 (0.0)	0 (0.0)	45 (73.8)
Usual activities	61	15 (24.6)	0 (0.0)	1 (1.6)	45 (73.8)
Pain/discomfort	61	14 (23.0)	2 (3.3)	0 (0.0)	45 (73.8)
Anxiety/depression	61	12 (19.7)	4 (6.6)	0 (0.0)	45 (73.8)

The total n is the total number of patients with non-missing value for that dimension at the corresponding time point.
The percentages are based on the respective total N in that row for each time point.
Abbreviations: EQ-5D: EuroQol 5-Dimensions; EQ-5D-3L: EuroQoL 5-Dimensions 3-Levels; FAS: full analysis set.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022).[15]

B18. CS, Section B.2.6.3, pages 65 and 54. Section B.2.6.3 of the CS states that in ENSIGN, the median duration of response (DoR) was 10.97 months. However, CS Section B.2.6.2 (Table 12) states that the median DoR in ENSIGN was not estimable. Please clarify which is correct.

The median DoR in ENSIGN should be “not estimable”, as per Table 12 of Section B.2.6.2 of the CS.[12] This was incorrectly reported as 10.97 months in Section B.2.6.3 of the CS.

B19. Priority. CS, Section B.2.6.3, Figure 14, page 70: Please comment on the possible reasons for the late OS events in ENSIGN (i.e., up to month 42).

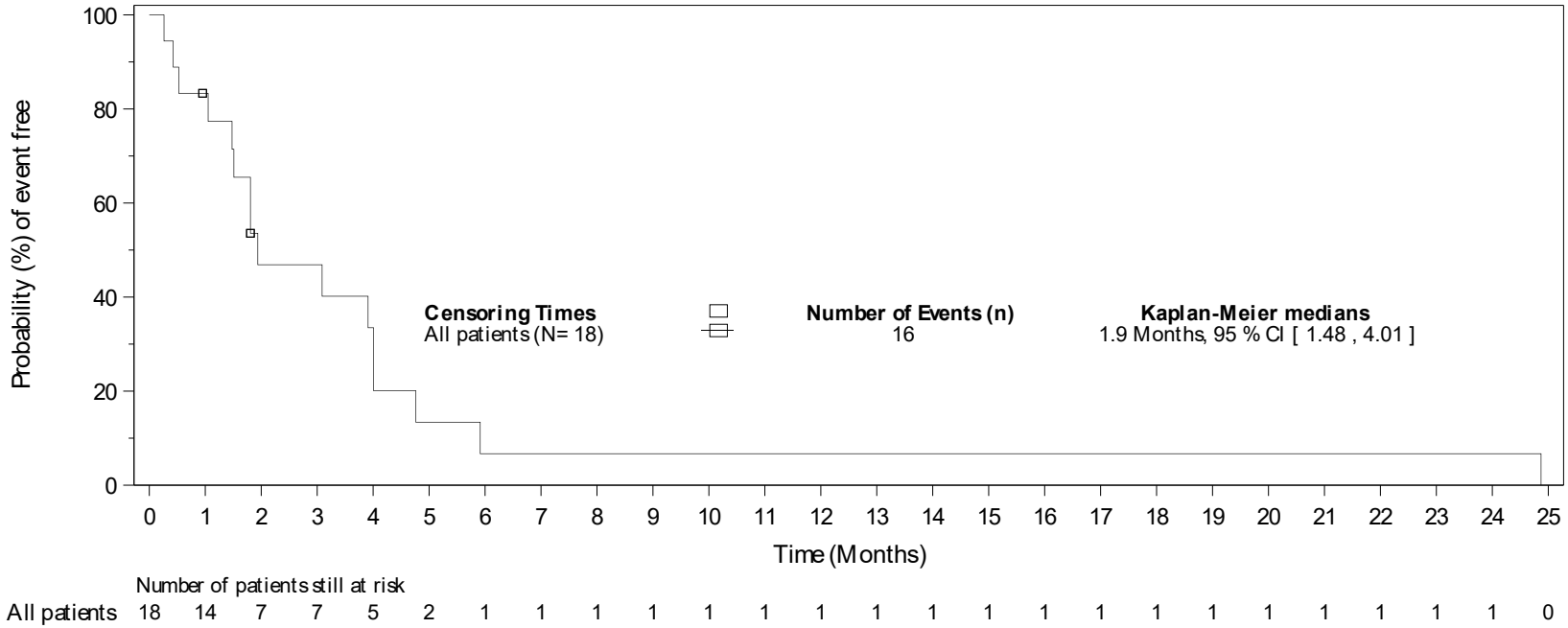
Whilst many patients may be expected to be cured following treatment with tisagenlecleucel, the nature of ALL means that patients may not respond to treatment, or subsequently relapse. Given that there were no deaths due to reasons other than the underlying cancer in patients achieving CR or CRi, disease relapse following initial and lasting response appears to be principal driver of late events seen in ENSIGN.[12] However, OS events may occur for various reasons, and speculation as to the nature and cause of OS events should be interpreted with caution, particularly when considering the small number of patients at risk at later timepoints in the ENSIGN trial.[12]

Notably, the NHSE CDF report has a larger sample size than the tisagenlecleucel trials, and demonstrates that median OS has not been reached.[5] OS at 24 months and 36 months at 72% [95% CI: 62%, 80%] and 67% [95% CI: 55%, 77%] respectively, thus showing that a proportion of patients can experience long periods of remission or cure.[5]

B20. Priority. CS, Section B.2.6. In TA554, the company provided a Kaplan-Meier plot for OS in patients who were not infused with tisagenlecleucel in ELIANA (see TA554 Committee Papers, EAG report, Figure 21). Please provide this plot using the latest available data cut-off. Please also provide equivalent plots using the latest available data cut-offs in ENSIGN and B2101J, and for the pooled dataset.

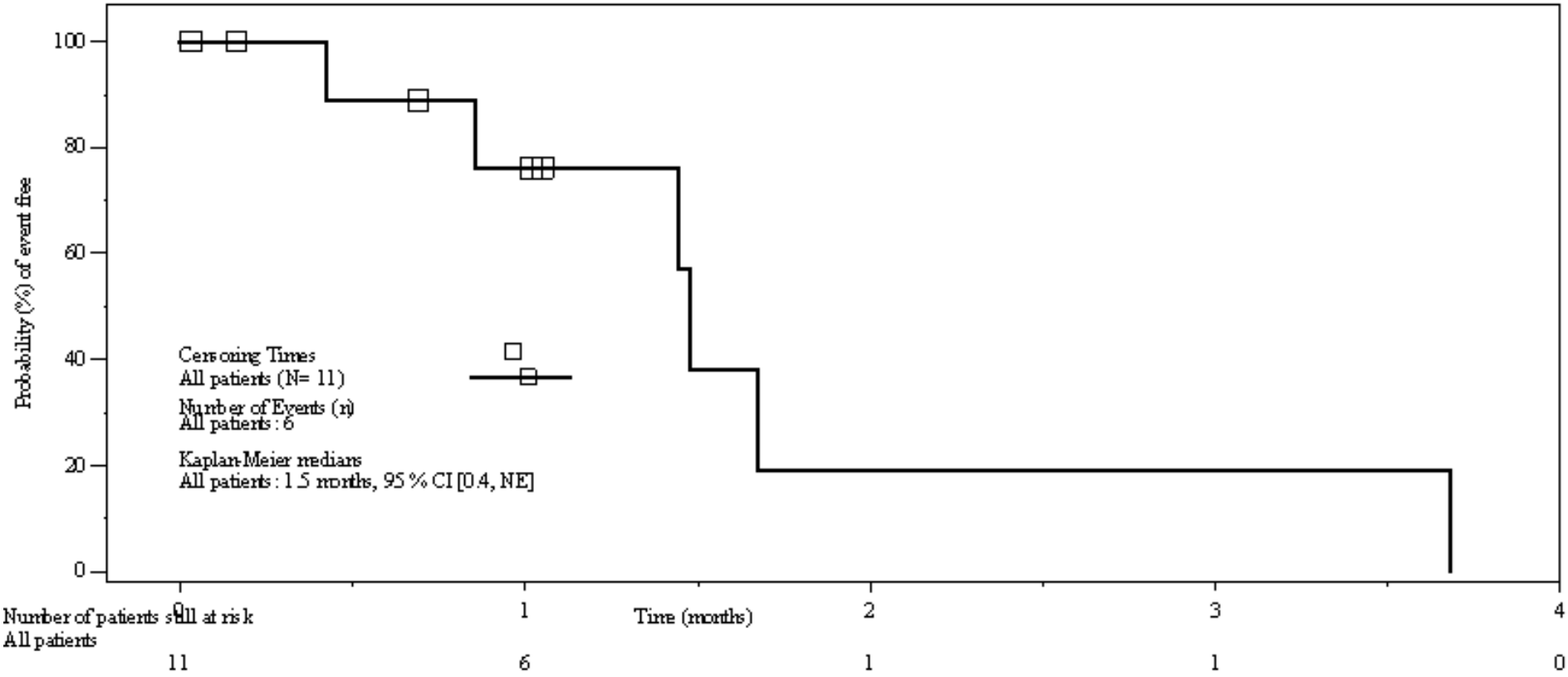
Kaplan–Meier curves (with the number of patients at risk at each time point) for OS for the ELIANA, ENSIGN and B2101J clinical trials (DCO; 31st Dec 2017, 24th May 2019 and 30th Jan 2017 respectively) for patients who were enrolled but not successfully infused with tisagenlecleucel are provided below.[12, 22, 23] As data on the non-infused population were not captured for later data cut-offs for the ELIANA and B2101J trials, the KM curves presented are based on earlier data cut-offs for these trials.

Figure 8: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel in ELIANA



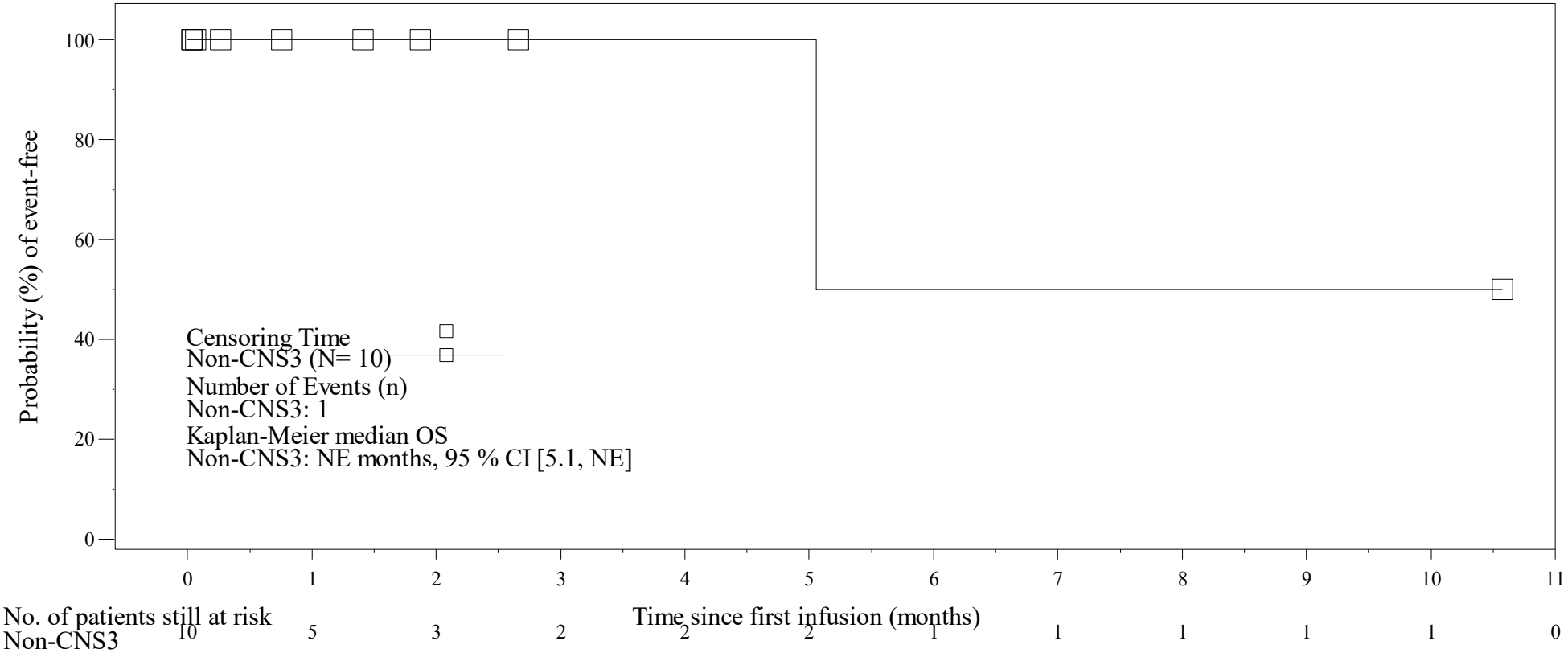
Abbreviations: CI: confidence interval; OS: overall survival.
Source: Novartis Data on File (2023; ELIANA DCO: 31st Dec 2017).[15]

Figure 9: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel in ENSIGN



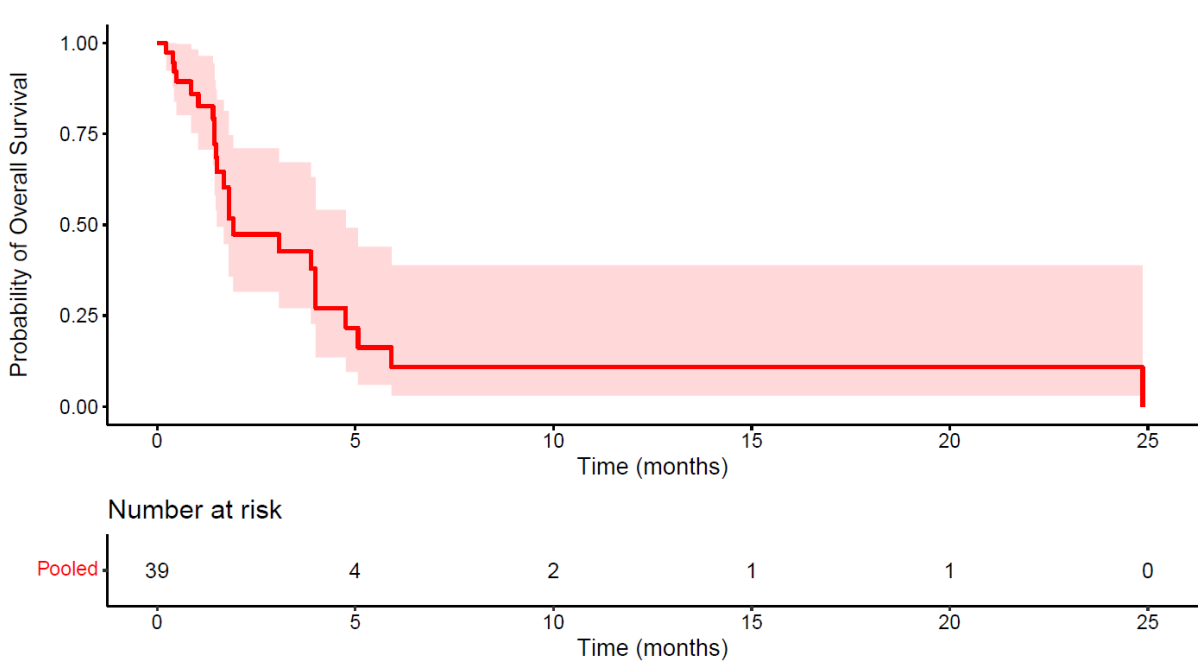
Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival.
Source: Novartis Data on File (2023; ENSIGN DCO: 24th May 2019).[15]

Figure 10: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel in B2101J



Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival.
Source: Novartis Data on File (2023; B2101J DCO: 30th Jan 2017).[15]

Figure 11: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel for pooled dataset

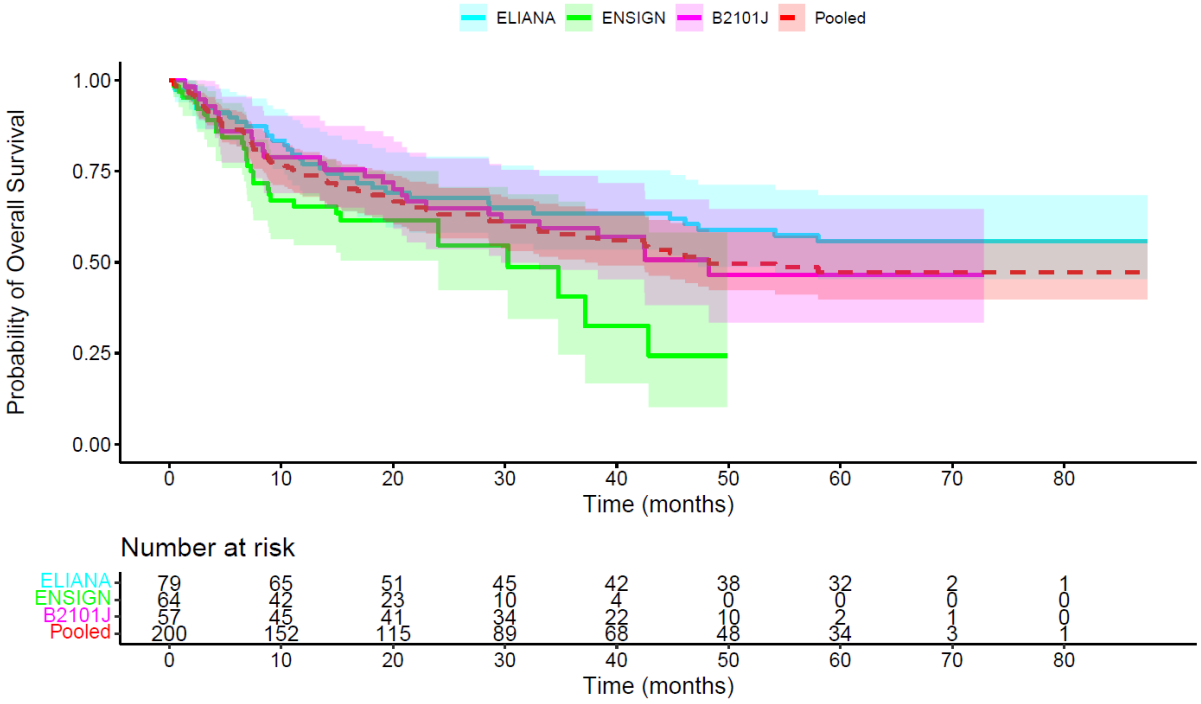


Abbreviations: OS: overall survival.
Source: Novartis Data on File (2023; ELIANA DCO: 31st Dec 2017, ENSIGN DCO: 24th May 2019, B2101J DCO: 30th Jan 2017).[15]

B21. Priority. CS, Section B.2.6, pages 54 to 80. Please provide Kaplan-Meier plots for OS for ELIANA, ENSIGN and B2101J, and for the pooled dataset, with and without censoring for subsequent allo-SCT.

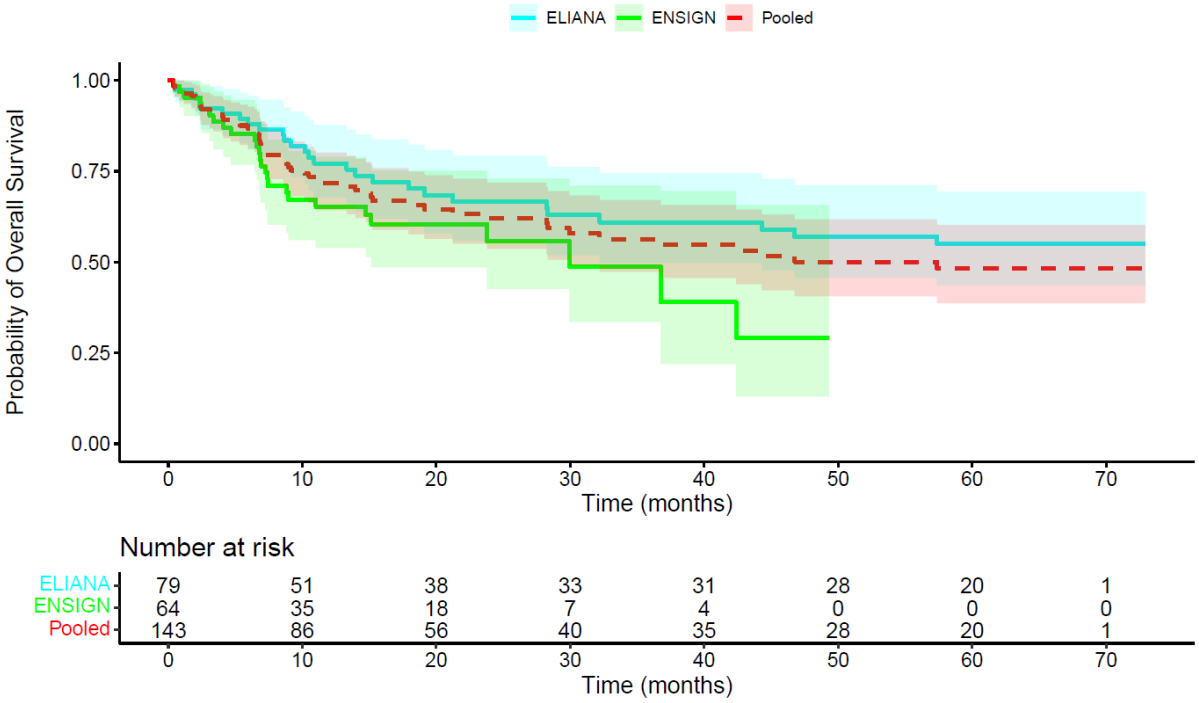
The Kaplan-Meier plot for OS without censoring for subsequent allo-SCT is presented in Figure 12 and the plot for OS with censoring for subsequent allo-SCT is presented in Figure 13.

Figure 12: Kaplan-Meier curve for OS without censoring for subsequent allo-SCT



Abbreviations: allo-SCT: allogeneic stem cell transplantation; OS: overall survival.
Footnote: B2101J was not included in this plot as no data for OS without censoring were available.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019; B2101J DCO: 7th May 2018).[15]

Figure 13: Kaplan-Meier curve for OS with censoring for subsequent allo-SCT



Abbreviations: allo-SCT: allogeneic stem cell transplantation; OS: overall survival.
Footnote: B2101J was not included in this plot as no data for OS with censoring were available from this study.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019).[15]

B22 CS Section B.2.8, Table 20, page 78. The table appears to contain an error – for ENSIGN, the table should say 56.2% no prior SCT. Please confirm whether this is correct.

Yes, Table 20 should reflect 56.2% for no prior SCT in the ENSIGN trial, as reported in Table 7 of the CS.[12]

B23. Priority. CS, Section B.2.6 and B.2.8, pages 54 to 80. The CS states that there is a plateau for EFS from 24 months in ELIANA, from 15 months in ENSIGN and from 28 months in B2101J. The CS also states that there is a plateau for OS from 24 months in ELIANA. However, based on the plots for all three trials in Figure 20 (EFS) and Figure 21 (OS), there appear to be continuing EFS and OS events in all three trials up to the point at which few patients remain. Please comment on this.

The emergence of a plateau denotes a visible reduction in the rates of events observed, to a period in the survival curve where the estimated survival probability remains relatively constant. Whilst the exact timepoint at which a plateau occurs is subjective, there is a clear reduction in the rate of observed EFS events in each tisagenlecleucel trial, and in OS events from Month 24 onwards in ELIANA.[12] Despite a small number of events occurring past these timepoints, the Company maintains that these reductions represent a plateau in survival, demonstrating that a number of patients can expect long-term survival following treatment with tisagenlecleucel amounting to a cure.

B24. CS, Section B.2.12, pages 104 to 108. The CS provides summary data for patients receiving tisagenlecleucel during the managed access period, captured in the NHSE CDF report. Data on percentage receiving subsequent allo-SCT are also provided from this report. Please provide text and/or tables summarising this report, in terms of the patient characteristics and the main results.

Summary data and text relating to patient characteristics and efficacy results from the NHSE CDF report are reported directly within the report itself, which has been included in the reference pack provided alongside the CS (please refer to the file named “TA554_Tisagenlecleucel_r-rALL_ SACT Report_26th Sept 2023”).[5]

B25. Priority. CS, Section B.3.2.3, Table 33, page 125. The table presents data on the proportion of infused patients who received a subsequent allo-SCT in ELIANA. Please also provide:

- The proportion of infused patients who received a subsequent allo-SCT in ENSIGN, B2101J and the pooled population.

- For all three studies and the pooled population, the proportion of infused patients in each study who received a subsequent allo-SCT (i) as consolidation therapy following tisagenlecleucel (i.e., not due to further relapse) and (ii) after further relapse following tisagenlecleucel.

Table 10 shows the proportion of patients who received allo-SCT in the tisagenlecleucel trials and pooled analysis, along with patients' disease status at the point of receipt of allo-SCT.

Table 10: Breakdown of infused patients who received a subsequent allo-SCT in ELIANA, ENSIGN, B2101J and pooled dataset

n (%)		ELIANA (safety analysis set) (N=79)	ENSIGN (full analysis set) (N=64)	B2101J (full analysis set) (N=57)	Pooled dataset (N=200)
Patients receiving subsequent allo-SCT		18 (22.78)[a]	9 (14.06)	8 (14.03)	35[a]
Disease status at allo-SCT	**CR**	16[a]	8 (12.50)	7 (12.28)	31[a]
	RD	4[a]	0 (0)	0 (0)	4[a]
	Unknown	0	1 (1.56)	1 (1.75)	2[a]

[a]Two patients in the ELIANA trial received allo-SCT twice following tisagenlecleucel. Of which, one patient received both rounds of allo-SCT in CR and the other patient received the first round of allo-SCT in CR and the second round allo-SCT in RD.
Abbreviations: allo-SCT: allogenic stem cell transplant; CR: complete remission; DCO: data cut-off; RD: relapsed disease.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 7th May 2018.[13]

B26. Priority. CS, Section B.2.10.2. The following questions relate to the safety data:

- Table 28, pages 96-98 and Table 29, pages 100-102. Regarding AEs across all tisagenlecleucel studies, the list of AEs from Table 28 is shorter than those from Table 22 of the CS in TA554. Please explain why this is the case.

Table 28 of CS lists the AEs reported in ≥10% of patients for ELIANA and ENSIGN and ≥30% of patients for B2101J as per thresholds specified in the respective trial CSRs. However, Table 22 of CS in TA554 lists the AEs reported in ≥10% of patients in ELIANA, ENSIGN and B2101J and therefore reports additional AEs which were recorded in B2101J.

- Please state how many deaths in each of the tisagenlecleucel trials were considered related to tisagenlecleucel and the causes of any such deaths.

In the ELIANA trial, a total of 33 deaths were recorded following tisagenlecleucel infusion of which 2 patients died within 30 days post-tisagenlecleucel infusion.[15, 21] Of these 2 deaths, one was considered to be potentially related to tisagenlecleucel infusion.[15] On 1st Dec 2015, 14 days after the tisagenlecleucel infusion, the patient died due to the event (cerebral haemorrhage) and concurrent toxicity of thrombocytopenia and coagulopathy.[15] The Investigator considered ALL,

prior chemotherapy, thrombocytopenia, coagulopathy, abdominal compartment syndrome, continuous veno-venous hemofiltration (CVVH) and hypertension as other possible contributory factors for the event (cerebral haemorrhage).[15] 31 patients died more than 30 days post-tisagenlecleucel infusion.[4, 15] Of these 31 deaths, 2 were considered potentially related to tisagenlecleucel infusion wherein one was due to systemic mycosis and one due to viral encephalitis.[4, 15] No deaths due to tisagenlecleucel were reported in the ENSIGN or B2101J trials.[12]

- For Tables 28 (AEs) and 29 (SAEs), please also provide data on the pooled AE incidence across all three trials.

The incidence of AEs and SAEs for the pooled data is presented below in Table 11 and Table 12 respectively.

Table 11: Summary of AEs reported in ≥10% of patients post-tisagenlecleucel infusion, regardless of study drug relationship (safety set)

	Pooled dataset (safety set) (N=200)		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one AE	200 (100.0)	41 (20.5)	145 (72.5)
CRS	162 (81.0)	37 (18.5)	46 (23.0)
Pyrexia	80 (40.0)	16 (8.0)	3 (1.5)
Decreased appetite	91 (45.5)	42 (21.0)	2 (1.0)
Hypogammaglobulinaemia	102 (51.0)	11 (5.5)	0
Febrile neutropenia	96 (48.0)	85 (42.5)	11 (5.5)
Headache	94 (47.0)	13 (6.5)	0
Anaemia	52 (26.0)	28 (14.0)	1 (0.5)
Vomiting	97 (48.5)	8 (4.0)	0
Platelet count decreased	94 (47.0)	18 (9.0)	40 (20.0)
White blood cell count decreased	113 (56.5.0)	32 (16.0)	52 (26.0)
Hypotension	69 (34.5)	18 (9.0)	31 (15.5)
Neutrophil count decreased	104 (52.0)	22 (11.0)	64 (32.0)
Diarrhoea	82 (41.0)	5 (2.5)	0
Nausea	89 (44.5)	15 (7.5)	0
Hypokalaemia	39 (19.5)	17 (8.5)	3 (1.5)
Hypoxia	30 (15.0)	14 (7.0)	9 (4.5)
Aspartate aminotransferase increased	81 (40.5)	28 (14.0)	11 (5.5)
Cough	69 (34.5)	0	0
Alanine aminotransferase increased	80 (40.0)	34 (17.0)	4 (2.0)
Hypophosphataemia	28 (14.0)	15 (7.5)	2 (1.0)
Lymphocyte count decreased	33 (16.5)	17 (8.5)	10 (5.0)
Tachycardia	59 (29.5)	4 (2.0)	2 (1.0)
Fatigue	57 (28.5)	1 (0.5)	0
Hypocalcaemia	16 (8.0)	5 (2.5)	0

Hypertension	28 (14.0)	6 (3.0)	0
Pain in extremity	28 (14.0)	1 (0.5)	0
Constipation	21 (10.5)	0	0
Anxiety	21 (10.5)	3 (1.5)	0
Blood bilirubin increased	21 (10.5)	12 (6.0)	0
Acute kidney injury	21 (10.5)	7 (3.5)	8 (4.0)
Pulmonary oedema	19 (9.5)	10 (5.0)	3 (1.5)
Upper respiratory tract infection	22 (11.0)	4 (2.0)	0
Abdominal pain	40 (20.0)	5 (2.5)	0
Hypoalbuminaemia	11 (5.5)	1 (0.5)	0
Neutropenia	22 (11.0)	5 (2.5)	15 (7.5)
Back pain	10 (5.0)	3 (1.5)	0
Myalgia	10 (5.0)	0	0
Hyperuricaemia	9 (4.5)	1 (0.5)	0
International normalised ratio increased	18 (9.0)	1 (0.5)	0
Nasal congestion	9 (4.5)	0	0
Thrombocytopenia	19 (9.5)	6 (3.0)	12 (6.0)
Arthralgia	12 (6.0)	1 (0.5)	0
Delirium	8 (4.0)	3 (1.5)	0
Disseminated intravascular coagulation	8 (4.0)	3 (1.5)	0
Encephalopathy	8 (4.0)	4 (2.0)	0
Hyperglycaemia	9 (4.5)	5 (2.5)	0
Pleural effusion	17 (8.5)	4 (2.0)	1 (0.5)
Rhinovirus infection	9 (4.5)	2 (1.0)	0
Serum ferritin increased	8 (4.0)	2 (1.0)	0
Tachypnoea	9 (4.5)	4 (2.0)	1 (0.5)
Dry skin	8 (4.0)	0	0
Face oedema	8 (4.0)	1 (0.5)	0
Oropharyngeal pain	8 (4.0)	0	0
Conjunctivitis	8 (4.0)	0	0
Blood creatinine increased	29 (14.5)	3 (1.5)	0
Prothrombin time prolonged	9 (4.5)	1 (0.5)	0
Chills	33 (16.5)	0	0
Epistaxis	10 (5.0)	4 (2.0)	1 (0.5)
Hyperphosphataemia	27 (13.5)	0	0
Rash	16 (8.0)	0	0
Haemoglobin decreased	53 (26.5)	13 (6.5)	4 (2.0)
Lymphopenia	47 (23.5)	19 (9.5)	20 (10.0)
Pain	27 (13.5)	7 (3.5)	0
Activated partial thromboplastin time prolonged	19 (9.5)	5 (2.5)	0

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; CSR: clinical study report.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN CSR (24th May 2019);[12] B2101J CSR (7th May 2018).[13]

Table 12: Summary of SAEs reported in at least two patients post-tisagenlecleucel infusion, regardless of study drug relationship (safety set)

	Pooled dataset (safety set) (N=200)		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one SAE	167 (83.5)	74 (37.0)	80 (40.0)
CRS	138 (69.0)	35 (17.5)	45 (22.5)
Febrile neutropenia	79 (39.5)	69 (34.5)	10 (5.0)
Hypotension	37 (18.5)	8 (4.0)	25 (12.5)
Pyrexia	27 (13.5)	3 (1.5)	0
Acute kidney injury	12 (6.0)	7 (3.5)	4 (2.0)
Hypoxia	17 (8.5)	9 (4.5)	6 (3.0)
Respiratory failure	9 (4.5)	0	8 (4.0)
Back pain	3 (1.5)	2 (1.0)	0
Cardiac arrest	4 (2.0)	0	4 (2.0)
Disseminated intravascular coagulation	10 (5.0)	5 (2.5)	0
Acute respiratory distress syndrome	6 (3.0)	0	6 (3.0)
Aspartate aminotransferase increased	2 (1.0)	2 (1.0)	0
Cardiac failure	2 (1.0)	1 (0.5)	1 (0.5)
Diarrhoea	4 (2.0)	1 (0.5)	0
Encephalitis	2 (1.0)	0	2 (1.0)
Viral encephalitis	2 (1.0)	1 (0.5)	1 (0.5)
Gastroenteritis	3 (1.5)	3 (1.5)	0
Herpes zoster	2 (1.0)	2 (1.0)	0
Mental status changes	3 (1.5)	1 (0.5)	0
Multiple organ dysfunction syndrome	3 (1.5)	0	3 (1.5)
Pancreatitis	2 (1.0)	2 (1.0)	0
Pleural effusion	5 (2.5)	2 (1.0)	2 (1.0)
Pneumonia	4 (2.0)	2 (1.0)	1 (0.5)
Respiratory distress	3 (1.5)	0	2 (1.0).
Respiratory syncytial virus infection	2 (1.0)	2 (1.0)	0
Rhinovirus infection	2 (1.0)	1 (0.5)	0
Septic shock	2 (1.0)	0	2 (1.0)
Staphylococcal bacteraemia	3 (1.5)	3 (1.5)	0
Tumour lysis syndrome	5 (2.5)	4 (2.0)	1 (0.5)
Upper respiratory tract infection	3 (1.5)	3 (1.5)	0
Clostridium difficile infection	3 (1.5)	1 (0.5)	0
Seizure	7 (3.5)	2 (1.0)	1 (0.5)
Encephalopathy	19 (9.5)	15 (7.5)	0
Neutropenia	3 (1.5)	0	3 (1.5)
Clostridium difficile colitis	2 (1.0)	0	0
Pulmonary oedema	2 (1.0)	1 (0.5)	1 (0.5)
Capillary leak syndrome	10 (5.0)	1 (0.5)	9 (4.5)

Dehydration	5 (2.5)	2 (1.0)	0
Left ventricular dysfunction	4 (2.0)	2 (1.0)	0
Coagulopathy	3 (1.5)	3 (1.5)	0
Device related infection	2 (1.0)	1 (0.5)	1 (0.5)
Headache	4 (2.0)	3 (1.5)	0
Sepsis	4 (2.0)	1 (0.5)	3 (1.5)
Candida infection	2 (1.0)	0	1 (0.5)
Hemophagocytic lymphohistiocytosis	2 (1.0)	0	2 (1.0)
Urinary tract infection	2 (1.0)	1 (0.5)	0

Abbreviations: CRS: cytokine release syndrome; CSR: clinical study report; SAE: serious adverse event.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN CSR (24th May 2019);[12] B2101J CSR (7th May 2018).[13]

- Please provide tables of: (a) AEs, including grade 3/4 AEs, suspected to be related to tisagenlecleucel and (b) SAEs suspected to be related to tisagenlecleucel, for all three trials and pooled across trials. The CS page 99 states that these data are provided in Appendix F but they are not.

The incidence of (a) AEs, including grade 3/4 AEs, suspected to be related to tisagenlecleucel and in more than 10% of patients (b) SAEs suspected to be related to tisagenlecleucel in at least two patients anytime post-tisagenlecleucel infusion, for all three trials and pooled across trials are presented below in Table 13 and Table 14 respectively.

Table 13: Summary of AEs reported in ≥10% of patients anytime post-tisagenlecleucel infusion, suspected to be related to tisagenlecleucel (safety set)

	ELIANA (safety set) (N=79)			ENSIGN (safety set) (N=64)			B2101J (safety set) (N=57)			Pooled data (safety set) (N=200)		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one AE	75 (94.9)	20 (25.3)	39 (49.4)	62 (96.9)	18 (28.1)	34 (53.1)	57 (100)	11 (19.3)	44 (77.2)	194 (97.0)	49 (24.5)	117 (58.5)
CRS	61 (77.2)	17 (21.5)	21 (26.6)	50 (78.1)	8 (12.5)	11 (17.2)	51 (89.5)	12 (21.1)	14 (24.6)	162 (81.0)	37 (18.5)	46 (23.0)
Hyogammaglobulinaemia	29 (36.7)	4 (5.1)	0	30 (46.9)	5 (7.8)	0	38 (66.7)	0	0	97 (48.5)	9 (4.5)	0
Febrile neutropenia	20 (25.3)	19 (24.1)	1 (1.3)	21 (32.8)	21 (32.8)	0	45 (78.9)	37 (64.9)	8 (14.0)	86 (43.0)	77 (38.5)	1 (0.5)
Hypotension	20 (25.3)	7 (8.9)	7 (8.9)	14 (21.9)	6 (9.4)	7 (10.9)	29 (50.9)	3 (15.3)	15 (26.3)	63 (31.5)	16 (8.0)	29 (14.5)
Pyrexia	19 (24.1)	5 (6.3)	2 (2.5)	17 (26.6)	4 (6.3)	1 (1.6)	19 (33.3)	1 (1.8)	0	55 (27.5)	10 (5.0)	3 (1.5)
Decreased appetite	16 (20.3)	6 (7.6)	2 (2.5)	19 (29.7)	10 (15.6)	0	37 (64.9)	19 (33.3)	0	72 (36.0)	35 (17.5)	2 (1.0)
Tachycardia	16 (20.3)	2 (2.5)	1 (1.3)	11 (17.2)	1 (1.6)	0	26 (45.6)	0	1 (1.8)	53 (26.5)	3 (1.5)	2 (1.0)
White blood cell count decreased	15 (19.0)	0	10 (12.7)	27 (42.2)	9 (14.1)	13 (20.3)	54 (94.7)	19 (33.3)	16 (28.1)	96 (48.0)	28 (14.0)	39 (19.5)
Anaemia	13 (16.5)	3 (3.8)	0	16 (25.0)	8 (12.5)	0	-	-	-	29 (14.5)	11 (5.5)	0
Headache	13 (16.5)	2 (2.5)	0	16 (25.0)	1 (1.6)	0	42 (73.7)	7 (12.3)	0	71 (35.5)	10 (5.0)	0
Hypoxia	13 (16.5)	5 (6.3)	5 (6.3)	9 (14.1)	4 (6.3)	2 (3.1)	13 (22.8)	7 (12.3)	3 (5.3)	35 (17.5)	16 (8.0)	10 (5.0)

Platelet count decreased	13 (16.5)	3 (3.8)	5 (6.3)	15 (23.4)	1 (1.6)	9 (14.1)	50 (87.8)	8 (14.0)	18 (31.6)	78 (39.0)	12 (6.0)	32 (16.0)
Aspartate aminotransferase increased	12 (15.2)	5 (6.3)	2 (2.5)	17 (26.6)	7 (10.9)	4 (6.3)	41 (71.9)	12 (21.1)	4 (7.0)	70 (35.0)	24 (12.0)	10 (5.0)
Lymphocyte count decreased	12 (15.2)	7 (8.9)	4 (5.1)	13 (20.3)	6 (9.4)	2 (3.1)	-	-	-	25 (12.5)	13 (6.5)	6 (3.0)
Nausea	12 (15.2)	1 (1.3)	0	21 (32.8)	3 (4.7)	0	41 (71.9)	7 (12.3)	0	74 (37.0)	11 (5.5)	0
Neutrophil count decreased	12 (15.2)	2 (2.5)	7 (8.9)	22 (34.4)	3 (4.7)	16 (25.0)	51 (89.5)	14 (24.6)	25 (43.9)	85 (42.5)	19 (9.5)	48 (24.0)
Alanine aminotransferase increased	11 (13.9)	4 (5.1)	0	18 (28.1)	11 (17.2)	0	41 (71.9)	13 (22.8)	4 (7.0)	70 (35.0)	28 (14.0)	4 (2.0)
Blood bilirubin increased	11 (13.9)	8 (10.1)	0	-	-	-	14 (24.6)	5 (8.8)	0	25 (12.5)	13 (6.5)	0
Hypophosphataemia	10 (12.7)	5 (6.3)	1 (1.3)	-	-	-	13 (22.8)	11 (19.3)	1 (1.8)	23 (11.5)	16 (8.0)	2 (1.0)
Vomiting	10 (12.7)	0	0	19 (29.7)	1 (1.6)	0	42 (73.7)	4 (7.0)	0	71 (35.5)	5 (2.5)	0
Acute kidney injury	9 (11.4)	3 (3.8)	4 (5.1)	-	-	-	6 (10.5)	2 (3.5)	0	15 (7.5)	5 (2.5)	4 (2.0)
Fatigue	9 (11.4)	0	0	12 (18.8)	0	0	25 (43.9)	0	0	46 (23.0)	0	0
Hypocalcaemia	9 (11.4)	3 (3.8)	0	-	-	-	8 (14.0)	7 (12.3)	0	17 (8.5)	10 (5.0)	0
Hypokalaemia	9 (11.4)	6 (7.6)	0	-	-	-	10 (17.6)	7 (12.3)	3 (5.3)	19 (9.5)	13 (6.5)	3 (1.5)
Pulmonary oedema	9 (11.4)	4 (5.1)	1 (1.3)	-	-	-	-	-	-	9 (4.5)	4 (2.0)	1 (0.5)
Abdominal pain	8 (10.1)	2 (2.5)	0	-	-	-	18 (31.6)	2 (3.5)	0	26 (13.0)	4 (2.0)	0

Diarrhoea	8 (10.1)	0	0	9 (14.1)	0	0	30 (52.6)	0	0	47 (23.5)	0	0
Neutropenia	8 (10.1)	0	7 (8.9)	7 (10.9)	3 (4.7)	0	-	-	-	15 (7.5)	3 (1.5)	7 (3.5)
Pleural effusion	8 (10.1)	2 (2.5)	1 (1.3)	-	-	-	7 (12.3)	0	1 (1.8)	15 (7.5)	2 (1.0)	2 (1.0)
Chills	-	-	-	7 (10.9)	0	0	20 (35.1)	0	0	27 (13.5)	0	0
Blood creatinine increased	-	-	-	9 (14.1)	2 (3.1)	0	20 (35.1)	1 (1.8)	0	29 (14.5)	3 (1.5)	0
International normalised ratio increased	-	-	-	8 (12.5)	0	0	14 (24.6)	2 (3.5)	0	22 (11.0)	2 (1.0)	0
Prothrombin time prolonged	-	-	-	8 (12.5)	1 (1.6)	0	-	-	-	8 (4.0)	1 (0.5)	0
Hyperphosphataemia	-	-	-	8 (12.5)	0	0	19 (33.3)	0	0	27 (13.5)	0	0
Cough	-	-	-	9 (14.1)	0	0	25 (43.9)	0	0	34 (17.0)	0	0
Lymphopenia	-	-	-	-	-	-	46 (80.7)	19 (33.3)	19 (33.3)	46 (23.0)	19 (9.5)	19 (9.5)
Sinus tachycardia	-	-	-	-	-	-	12 (21.1)	1 (1.8)	1 (1.8)	12 (6.0)	1 (0.5)	1 (0.5)
Constipation	-	-	-	-	-	-	7 (12.3)	0	0	7 (3.5)	0	0
Pain	-	-	-	-	-	-	25 (43.9)	6 (10.5)	0	25 (12.5)	6 (3.0)	0
Hyperbilirubinemia	-	-	-	-	-	-	10 (17.5)	1 (1.8)	0	10 (5.0)	1 (0.5)	0
Sinusitis	-	-	-	-	-	-	7 (12.3)	0	0	7 (3.5)	0	0
Upper respiratory tract infection	-	-	-	-	-	-	6 (10.5)	0	0	6 (3.0)	0	0

Haemoglobin decreased	-	-	-	-	-	-	53 (93.0)	12 (21.1)	4 (7.0)	53 (26.5)	12 (6.0)	4 (3.5)
Activated partial thromboplastin time	-	-	-	-	-	-	19 (33.3)	5 (8.8)	0	19 (9.5)	5 (2.5)	0
Blood fibrinogen decreased	-	-	-	-	-	-	10 (17.5)	2 (3.5)	2 (3.5)	10 (5.0)	2 (1.0)	2 (1.0)
Blood uric acid increased	-	-	-	-	-	-	9 (15.8)	0	1 (1.8)	9 (4.5)	0	1 (0.5)
Metabolic acidosis	-	-	-	-	-	-	8 (14.0)	6 (10.5)	0	8 (4.0)	6 (3.0)	0
Hyperuricaemia	-	-	-	-	-	-	7 (12.3)	0	0	7 (3.5)	0	0
Hyperglycaemia	-	-	-	-	-	-	6 (10.5)	4 (7.0)	0	6 (3.0)	4 (2.0)	0
Myalgia	-	-	-	-	-	-	10 (17.5)	0	0	10 (5.0)	0	0
Pain in extremity	-	-	-	-	-	-	10 (17.5)	1 (1.8)	0	10 (5.0)	1 (0.5)	0
Arthralgia	-	-	-	-	-	-	6 (10.5)	0	0	6 (3.0)	0	0
Encephalopathy	-	-	-	-	-	-	15 (26.3)	13 (22.8)	0	15 (7.5)	13 (6.5)	0
Dizziness	-	-	-	-	-	-	10 (17.5)	0	0	10 (5.0)	0	0
Confusional state	-	-	-	-	-	-	12 (21.1)	0	0	12 (6.0)	0	0
Rhinorrhoea	-	-	-	-	-	-	12 (21.1)	0	0	12 (6.0)	0	0
Epistaxis	-	-	-	-	-	-	10 (17.5)	3 (5.3)	0	10 (5.0)	3 (1.5)	0
Tachypnoea	-	-	-	-	-	-	10 (17.5)	0	0	10 (5.0)	0	0

Nasal congestion	-	-	-	-	-	-	9 (15.8)	0	0	9 (4.5)	0	0
Petechiae	-	-	-	-	-	-	7 (12.3)	0	0	7 (3.5)	0	0
Rash papular	-	-	-	-	-	-	6 (10.5)	0	0	6 (3.0)	0	0
Hypertension	-	-	-	-	-	-	11 (19.3)	3 (5.3)	0	11 (5.5)	3 (1.5)	0
Capillary leak syndrome	-	-	-	-	-	-	10 (17.5)	1 (1.8)	9 (15.8)	10 (5.0)	1 (0.5)	9 (4.5)

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; DCO: data cut-off.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 7th May 2018).[15]

Table 14: Summary of SAEs reported in at least two patients anytime post-tisagenlecleucel infusion, suspected to be related to tisagenlecleucel (safety set)

	ELIANA (safety set) (N=79)			ENSIGN (safety set) (N=64)			B2101J (safety set) (N=57)			Pooled data (safety set) (N=200)		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one SAE	53 (67.1)	20 (25.3)	28 (35.4)	46 (71.9)	20 (31.3)	16 (25.0)	49 (86.0)	27 (47.4)	19 (33.3)	148 (74.0)	67 (33.5)	63 (31.5)
CRS	50 (63.3)	16 (20.3)	21 (26.6)	41 (64.1)	8 (12.5)	10 (15.6)	47 (82.5)	11 (19.3)	14 (24.6)	138 (69.0)	35 (17.5)	45 (22.5)
Febrile neutropenia	13 (16.5)	12 (15.2)	1 (1.3)	20 (31.3)	20 (31.3)	0	41 (71.9)	33 (57.9)	8 (14.0)	74 (37.0)	65 (32.5)	9 (4.5)
Hypotension	8 (10.1)	2 (2.5)	6 (7.6)	6 (9.4)	3 (4.7)	3 (4.7)	21 (36.8)	3 (5.3)	15 (26.3)	35 (17.5)	8 (4.0)	24 (12.0)
Acute kidney injury	4 (5.1)	2 (2.5)	2 (2.5)	3 (4.7)	2 (3.1)	1 (1.6)	3 (5.3)	2 (3.5)	0	10 (5.0)	6 (3.0)	3 (1.5)
Pyrexia	3 (3.8)	0	0	2 (3.1)	0	0	11 (19.3)	1 (1.8)	0	16 (8.0)	1 (0.5)	0

Encephalitis	2 (2.5)	0	2 (2.5)	-	-	-	-	-	-	2 (1.0)	0	2 (1.0)
Encephalitis viral	2 (2.5)	1 (1.3)	1 (1.3)	-	-	-	-	-	-	2 (1.0)	1 (0.5)	1 (0.5)
Herpes zoster	2 (2.5)	2 (2.5)	0	-	-	-	-	-	-	2 (1.0)	2 (1.0)	0
Hypoxia	2 (2.5)	1 (1.3)	1 (1.3)	4 (6.3)	1 (1.6)	1 (1.6)	7 (12.3)	4 (7.0)	3 (5.3)	13 (6.5)	6 (3.0)	5 (2.5)
Multiple organ dysfunction syndrome	2 (2.5)	0	2 (2.5)	-	-	-	-	-	-	2 (1.0)	0	2 (1.0)
Pleural effusion	2 (2.5)	1 (1.3)	1 (1.3)	2 (3.1)	1 (1.6)	0	-	-	-	4 (2.0)	2 (1.0)	0
Respiratory failure	2 (2.5)	0	2 (2.5)	2 (3.1)	0	2 (3.1)	-	-	-	4 (2.0)	0	4 (2.0)
Disseminated intravascular coagulation	-	-	-	2 (3.1)	0	0	5 (8.8)	3 (5.3)	0	7 (3.5)	3 (1.5)	0
Neutropenia	-	-	-	2 (3.1)	0	2 (3.1)	-	-	-	2 (1.0)	0	2 (1.0)
Encephalopathy	-	-	-	3 (4.7)	1 (1.6)	0	15 (26.3)	13 (22.8)	0	18 (9.0)	14 (7.0)	0
Seizure	-	-	-	2 (3.1)	1 (1.6)	0	3 (5.3)	0	1 (1.8)	5 (2.5)	1 (0.5)	1 (0.5)
Coagulopathy	-	-	-	-	-	-	3 (5.3)	3 (5.3)	0	3 (1.5)	3 (1.5)	0
Left ventricular dysfunction	-	-	-	-	-	-	4 (7.0)	2 (3.5)	0	4 (2.0)	2 (1.0)	0
Dehydration	-	-	-	-	-	-	3 (5.3)	1 (1.8)	0	3 (1.5)	1 (0.5)	0
Acute respiratory distress syndrome	-	-	-	-	-	-	4 (7.0)	0	4 (7.0)	4 (2.0)	0	4 (2.0)
Capillary leak syndrome	-	-	-	-	-	-	10 (17.5)	1 (1.8)	9 (15.8)	10 (5.0)	1 (0.5)	9 (4.5)

Abbreviations: CRS: cytokine release syndrome; DCO: data cut-off; SAE: serious adverse event.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 7th May 2018).[15]

- Please provide a table of AEs of special interest (AESI), for all three trials and pooled across trials. Please also provide some commentary on the clinical significance of these AESI and whether any led to death or long-term ill health. The EPAR and SmPC suggest that AESI include: CRS, febrile neutropenia, prolonged cytopenias, infections, neurological events, tumour lysis syndrome and hypogammaglobulinaemia, and secondary malignancies.

The table summarising AEs of special interest (AESIs) for all three trials and pooled across trials is presented below in Table 15. These AESIs include CRS, febrile neutropenia, haematological disorders including cytopenias infections, serious neurological adverse reactions, tumour lysis syndrome, hypogammaglobulinaemia and secondary malignancies. Reasons for death in each trial have been outlined in Section B.2.10.2 of the CS.

As noted in the European public assessment report (EPAR), these AESIs, especially CRS, infections and febrile neutropenia, are serious and can be life-threatening, and therefore need to be effectively and promptly managed.[24] The most commonly reported AESI across all three trials was CRS with an incidence of 77.2%, 78.1% and 89.5% in ELIANA, ENSIGN and B2101J respectively.[4, 12] None of the CRS events were fatal and were managed with the appropriate supportive care and systematic anti-cytokine therapy which included tocilizumab.[4, 12] As per Section B.2.10.2 of the CS, the trial estimate of ICU admission due to CRS is likely a conservative estimate of real world use following the emergence of evidence that disproves the initial belief that tocilizumab has a detrimental effect on the efficacy of CAR-T therapy. Tocilizumab is therefore now more readily administered which prevents CRS progression observed in patients.

Haematological disorders which include cytopenia and febrile neutropenia were also frequently reported across trials but reduced significantly in incidence during the >8 weeks to 1 year and > 1 year post-tisagenlecleucel infusion periods.[4, 12] Of note, the probability of resolution of cytopenias by Month 6 post-infusion in ELIANA ranged from 79.3% to 96.9. Similar high resolution rates were observed in both ENSIGN (range: 25.0% to 75.6%) and B2101J trials (range: 81.5% to 100%), indicating the effective resolution of these AESIs.[12]

Given the underlying disease and prior anticancer treatments received by the patient population, a high incidence of infections is anticipated, as observed in the infection rates ranging between 68.4% and 75.9% across all three trials.[4, 12]These infections were managed with supportive measures but their incidence remains fairly consistent within 8 weeks, during >8 weeks to 1 year and during > 1 year, signifying irreversible immunocompromised conditions, as expected in patients who have been exposed to multiple anticancer treatments.[4, 12] The incidence of infections is therefore not an artefact exclusive to tisagenlecleucel infusion.

Hypogammaglobulinaemia is however, an expected effect resultant from CAR-T therapy which may increase the risk of infections in patients. Incidence of hypogammaglobulinaemia was managed effectively with prophylactic intravenous immunoglobulin (IVIg) as per local guidelines. .[4, 12]The AESIs observed are expected in nature and therefore, treatment centres can be well-equipped to manage the onset of such AESIs should they occur.

Table 15: Summary of AESIs reported in ELIANA, ENSIGN, B2101J and the pooled dataset anytime post-tisagenlecleucel infusion (safety set)

	ELIANA (safety set) (N=79)			ENSIGN (safety set) (N=64)			B2101J (safety set) (N=57)[a]			Pooled data (safety set) (N=200)		
Preferred term	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one event	79 (100)	21 (26.6)	49 (62.0)	63 (98.4)	23 (35.9)	23 (35.9)	NR	NR	NR	142 (71.0)	44 (22.0)	72 (36.0)
CRS	61 (77.2)	17 (21.5)	21 (26.6)	50 (78.1)	8 (12.5)	11 (17.2)	51 (89.5)	12 (21.1)	14 (24.6)	162 (81.0)	37 (18.5)	46 (23.0)
Febrile neutropenia	27 (34.2)[b]	25 (31.6)[b]	2 (2.5)[b]	3 (4.7)[c]	3 (4.7)[c]	0[c]	45 (78.9)	37 (64.9)	8 (14.0)	75 (37.5)	65 (32.5)	10 (5.0)
Hematological disorders including cytopenias (total)	55 (69.6)	21 (26.6)	31 (39.2)	27 (42.2)[d]	10 (15.6)[d]	12 (18.8)[d]	NR[e]	NR[e]	NR[e]	82 (41.0)	31 (15.5)	43 (21.5)
Infection (total)	60 (75.9)	25 (31.6)	14 (17.7)	46 (71.9)	14 (21.9)	4 (6.3)	39 (68.4)	14 (24.6)	1 (1.8)	145 (72.5)	53 (26.5)	19 (9.5)
Serious neurological adverse reactions (total)	35 (44.3)	13 (16.5)	0	21 (32.8)	5 (7.8)	0	47 (82.5)[f]	18 (31.6)[f]	1 (1.8)[f]	103 (51.5)	36 (18.0)	1 (0.5)
Tumour lysis syndrome	5 (6.3)	4 (5.1)	1 (1.3)	2 (3.1)	2 (3.1)	0	3 (5.3)	3 (5.3)	0	10 (5.0)	9 (4.5)	1 (0.5)
Hypogammaglobulinaemia	32 (40.5)	6 (7.6)	0	32 (50.0)	5 (7.8)	0	38 (66.7)	0	0	102 (51.0)	11 (5.5)	0
Secondary malignancies	1 (1.3)	1 (1.3)	0	2 (3.1)	2 (3.1)	0	NR	NR	NR	3 (1.5)	3 (1.5)	0

[a]Unavailable from CSR for AESIs reported anytime post-tisagenlecleucel. Only AESIs reported within 8 weeks were tabulated. Values for B2101J have therefore been informed by AE incidence reported in B2101J as listed in Table 29 of CS. Total incidence of patients with at least one AESI of any grade within 8 weeks post tisagenlecleucel infusion was 51/57 (89.5%) with 28 Grade 3 events (49.1%) and 16 Grade 4 events (28.1%).
[b]Febrile neutropenia was counted as part of the total incidence for hematological disorders including cytopenias.
[c]Febrile neutropenia defined as part of hematopoietic cytopenias not resolved by Day 28.
[d]Defined as hematopoietic cytopenias not resolved by Day 28.
[e]Not reported in total, reported by individual parameters (i.e. white blood cells, hemoglobin).
[f]Reported as nervous system disorders.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN CSR (24th May 2019);[12] B2101J CSR (7th May 2018).[13]

- Please provide data on discontinuations due to AEs for all trials for: the pre-treatment period, during lymphodepleting chemotherapy, and post tisagenlecleucel infusion.

The requested data on discontinuations due to AEs in each trial period for the tisagenlecleucel studies are shown in Table 16 below.

Table 16: Summary of discontinuation due to AEs in ELIANA, ENSIGN and B2101J

Discontinuation due to AEs	ELIANA (N=97)	ENSIGN (N=75)	B2101J (N=57)
Pre-treatment period, n (%)	3 (3.1)	1 (1.3)	NR
During lymphodepleting chemotherapy, n (%)	0 (0)	0 (0)	NR
Post tisagenlecleucel infusion, n (%)	0 (0)	0 (0)	0 (0)

Abbreviations: AE: adverse event; CSR: clinical study report; DCO: data cut-off.
Source: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 7th May 2018).[15]

Indirect comparisons

B27. CS, Section B.2.9, page 81. The text states that *"No trials were identified for FLAG-IDA in paediatric patients with r/r B-cell ALL."* Please clarify whether any studies of FLAG-IDA in similar or related populations were identified, and if so, please provide justification for their exclusion.

The SLR was limited to paediatric patients with r/r B-cell ALL, therefore studies in other populations, for example adult populations or untreated ALL, would have been excluded at the abstract review stage. As noted in Section B.2.9 of the CS, within the population of interest in the SLR, no studies were identified for FLAG-IDA specifically, though six publications reporting on chemotherapy were identified and assessed for suitability as proxy evidence for FLAG-IDA.

B28. Priority. CS, Section B.2.9, pages 80-86. The CS presents a summary of the clinical evidence considered for FLAG-IDA (Tables 21 and 22), but the equivalent data are not presented for blinatumomab. Please provide a similar table for blinatumomab. For both comparators, please provide details within the tables on the justification for excluding each study.

The summary of clinical evidence considered for blinatumomab are presented below in Table 17 and Table 18. Table 17 presents the summary of clinical evidence which were identified in the March 2023 SLR update and prioritised for extraction due to their relevance to the indirect treatment comparisons and economic modelling. The reasons for not considering the Gore *et al.* (2018)[25] and Locatelli *et al.* (2022)[26] have been detailed in Section B.2.9 of the CS though included in the summary table below as requested.

Table 18 presents the summary of the von Stackelberg *et al.* (2016)[10] study which was accepted by the Committee in the original Company submission (TA554) as the efficacy data source for blinatumomab.[1] As mentioned in Section B.2.9 of the CS, given that the von Stackelberg *et al.* (2016)[10] study represents the pivotal clinical trial for blinatumomab in paediatric patients with r/r B-cell ALL and the lack of identification of new compelling data, as listed in Table 17 below, the von Stackelberg *et al.* (2016)[10] study was considered as the most appropriate efficacy data source for blinatumomab in the current submission.

Reasons for not considering the clinical evidence identified for FLAG-IDA as appropriate efficacy data sources have been outlined in Section B.2.9 of the CS.

Table 17: Clinical evidence identified and prioritised for data extraction in the March 2023 SLR update for the efficacy of blinatumomab

Author year	Study design	Number of ALL patients	Country	Patient population: age	Intervention	Patient population: line of relapse	Patient population: prior allo-SCT	Prior therapies	Median OS	Reasons for not considering evidence as efficacy data source
Gore *et al.* (2018)[25]	Phase I/II, open-label, multicentre, non-randomised	70 patients	International	• Patients aged ≤ 18 years • Median age at study entry: NR	Blinatumomab	2nd or further relapse	57.1% patients (40/70) with prior allo-SCT	NR	7.5 months	• The Gore *et al.* (2018) study reports on the same pivotal clinical trial as that reported by von Stackelberg *et al.* (2016), but data are only reported by allo-SCT use before or after blinatumomab and thus are not comparable to the full tisagenlecleucel trial populations.[10, 25]
Locatelli *et al.* (2022)[26]	Single-arm expanded open-access study	110 patients	International (16 centres in Europe and the United States)	• Patients aged >28 days and <18 years at time of enrolment • Median age (range) at study entry: 8.5 (0.4–17)	Blinatumomab	• 2nd or further relapse (61/110, 55%) • Relapse after allo-SCT (44/110, 40%)	44.1% patients (45/110) with prior allo-SCT	NR	• All patients: 14.6 months • MRD responders: not estimable • MRD non-responders: 9.3 months	• The Locatelli *et al.* (2022) study is an extension of the RIALTO study which was previously identified in the original SLR conducted in March 2018 as part of the original submission (TA554).[26] • A brief re-cap of the assessment performed in TA554 is as follows: The eligibility criteria of the RIALTO study

										permitted patients previously treated with blinatumomab, and therefore it was considered that some patients may have overlapped between the von Stackelberg *et al.* (2016) and RIALTO studies. For this reason, the RIALTO study had not been considered further in TA554 for inclusion within an indirect treatment comparison, nor was it considered appropriate to explore a pooling of the von Stackelberg *et al.* (2016) and RIALTO studies.[10]

Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogenic stem cell transplant; MRD: minimal residual disease; NR: not reported; OS: overall survival; SLR: systematic literature review; TA: technology appraisal.
Source: Gore *et al.* (2018);[25] Locatelli *et al.* (2022);[26] von Stackelberg *et al.* (2016).[10]

Table 18: Overview of the von Stackelberg *et al.* (2016) study identified and accepted as an efficacy data source for blinatumomab in the March 2018 SLR update as part of TA554

Author year	Study design	Number of ALL patients	Country	Patient population: age	Intervention	Patient population: line of relapse	Patient population: prior allo-SCT	Prior therapies	Median OS
von Stackelberg *et al.* (2016)[10]	Phase I/II, open-label, multicentre, non-randomised	70 patients	International (26 centres in Europe and US)	• Patients aged < 18 years (2–17 years in phase I dosage escalation) • Median age at study entry: 8 (<1–17)	Blinatumomab	• No relapse: 2/70 (3%) • 1st relapse: 31/70 (44%) • 2nd relapse: 29/70 (41%) • 3rd or further relapse: 8/70 (11%)	40/70 patients (57%) with prior allo-SCT	NR	7.5 months

Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogenic stem cell transplant; NR: not reported; OS: overall survival; SLR: systematic literature review; TA: technology appraisal.
Source: von Stackelberg *et al.* (2016).[10]

Please also consider including the TOWER study of blinatumomab as this includes some patients aged 18-35 years.

The TOWER study of blinatumomab was a phase III trial which enrolled Ph-ve B-cell ALL patients aged 18 and above, with a mean age of 40.8 years (range: 18–80).[27] The study results were first published in Kantarjian *et al.* (2017) and therefore would have been identified in the March 2018 SLR performed.[27] However, given that the publication does not report data separately for patients aged below 26 years, the study would have been reviewed and excluded at title/abstract review stage in the original SLR.

Consideration of the TOWER study to model the efficacy of blinatumomab was previously noted by the EAG in TA554.[1] However, the Committee explicitly stated that *"neither the ERG nor the Company presented a suitable alternative data source for the efficacy of blinatumomab, it was appropriate to consider von Stackelberg et al. in its decision-making".*[1] Von Stackelberg *et al.* (2016) was therefore retained as the source of efficacy and safety evidence for blinatumomab within the current submission.

B29. Priority. CS, Section B.2.9, page 87. The text states *"Baseline characteristics that are suspected to be effect modifying in nature were considered, with their relative importance for adjustment ranked based on previous consultation with clinicians and review of the literature."* Please clarify if this prioritisation exercise was restricted only to treatment effect modifiers, or whether prognostic factors were also as potential covariates for inclusion in the adjustment model.

Only treatment effect modifiers were considered for adjustment in the MAIC, whilst prognostic variables were not adjusted to avoid over-matching, in line with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support document (TSD) 18.[28]

B30. Priority. CS, Section B.3.3.2, page 128. The CS presents a MAIC for tisagenlecleucel against blinatumomab and salvage chemotherapy; however, the economic model relies on naïve indirect comparisons which assume no heterogeneity in prognostic factors or treatment effect modifiers between studies. Please justify this approach.

As stated in Section B.2.9 of the CS, given the lack of meaningful differences in efficacy estimates when adjusting for population differences across intervention and comparator trials, unadjusted ELIANA data were used in the economic analysis, in order to retain the largest sample sizes to inform efficacy outcomes in the model. The minor differences between the unadjusted and adjusted estimates can be found in Table 26, where the direction of association and statistical significance remained unchanged.

B31. CS, Section B.2.9, page 87. The text states that *"Versus the blinatumomab von Stackelberg et al. (2016) study, feedback from UK clinical experts was that it would be reasonable to conclude that patients in the blinatumomab trial were fitter based on the proportion refractory and those with >3 lines of prior therapy"*. Please comment on why the CTL019 matched curve is lower than the CTL019 unmatched curve in Figure 24, if the matched population was fitter than the unmatched population.

Yes, the matched population were seemingly fitter than the unmatched population on the basis of number of lines of previous lines of therapy and number of previous remissions/relapses. As seen in Table 24 in Section B.2.9 of the CS, the mean number of previous lines of therapy was lower in the matched population than unmatched population. Almost half (44.30%) of the unmatched population also had at least 3 previous remissions/relapses; however, this proportion was 11.43% in the matched population.

Links between the observations mentioned above and the shift in the KM curve due to the matching cannot be drawn directly as only treatment effect modifiers of greater importance variables were considered in the matching to prevent the loss of precision from over-matching of variables, as stated in Section B.2.9 of the CS. As such, there may be other underlying (prognostic) variables that could have an impact on OS.

Please also comment on whether patients in the blinatumomab trial population were fitter than the pooled tisagenlecleucel population.

Patients in the blinatumomab trial population may be considered fitter than the pooled tisagenlecleucel population. The majority (88.58%) of the blinatumomab trial population had less than 3 previous remissions/relapses as compared to 66% in the pooled tisagenlecleucel population.[10]

Please also report on the proportion of patients getting subsequent allo-SCT after adjustment in the MAIC.

The proportion of patients getting subsequent allo-SCT in the ELIANA population before and after adjustment was 22.78% and 30.51% respectively.[21]

B32. CS, Section B.2.9, page 81. Please comment on whether the patients in the salvage chemotherapy Jeha et al. (2006) study were fitter than the ELIANA study population and the pooled population (ELIANA, ENSIGN, B210J). Please also comment on whether this is reflected in the matched KM curve.

Comparing the number of previous remissions/relapses, the salvage chemotherapy population in the Jeha *et al.* (2006) study was fitter than the ELIANA study but less fit than the pooled population. The proportion of the patients in the salvage chemotherapy population who had less

than 3 previous remissions/relapses was 37.70% whilst those of the ELIANA and pooled populations were 32.91% and 66% respectively.[11, 12] However, as mentioned in the response to B31, links between these observations and the shift in KM curve due to the matching cannot be drawn directly as there may be other underlying (prognostic) variables that could have an impact on OS.

Please also report on the proportion of patients getting subsequent allo-SCT after adjustment in the MAIC.

The proportion of patients getting subsequent allo-SCT in the ELIANA population before and after adjustment was 22.78% and 32.09% respectively.[21]

B33. CS, Section B.2.9, page 88 to 89. If possible, please also include age as a covariate in the MAIC within the pooled population. Please report the effective sample size, a summary of baseline characteristics before and after adjustment, the distribution of weights and include this analysis in the economic model.

As per the original CS (TA554), age was not deemed by clinical experts as a critical variable attributing to outcome differences in the patient population. As presented in Appendix D.1.9 of the CS, adjustment for age would have resulted in minimal differences (before: 12.03 vs after: 11.87) and therefore, to prevent the loss of precision from over-matching of variables, age was not considered a covariate in the MAIC within the pooled population.

B34. Priority. CS, Section B.2.9, page 80. The final guidance document for TA554 states that *"The committee accepted that both Jeha et al. and Kuhlen et al. had a number of limitations, but concluded that that it was appropriate to consider both studies in its decision-making."* Please clarify why Kuhlen has not been included the economic analysis. Please amend the model to allow for comparisons using the Kuhlen data, as was done in TA554.

As noted in Section B.2.9 of the CS, Kuhlen *et al.* (2017) is associated with substantial limitations and is not reflective of the patient population eligible for tisagenlecleucel.

- All patients in the Kuhlen *et al*. (2017) study had received a prior SCT.[29] This compares to 60.8% in ELIANA,[4] and only 31% reported in the NHSE CDF report for tisagenlecleucel.[5] The Kuhlen *et al*. (2017) study therefore represents only a small subset of patients, those having received prior SCT, likely to receive tisagenlecleucel in NHS practice
- The Kuhlen *et al*. (2017) study only recruited patients having relapsed following complete remission, excluding any patients refractory to initial treatment,[29] unlike the tisagenlecleucel trials
- The Kuhlen *et al*. (2017) study included patients with extramedullary relapse (19.7%),[29] who have been shown to have better EFS and OS outcomes than patients with bone

marrow relapse. Patients with extramedullary relapse were excluded from the tisagenlecleucel trials. Any comparison informed by Kuhlen *et* al. (2017) data may therefore be biased by this difference in inclusion criteria

- The Kuhlen *et al*. (2017) study included patients with T-cell ALL (21.4%),[29] who would not be eligible for tisagenlecleucel under its license

Whilst acknowledging the limitations of the Jeha *et al*. study (2006) chosen to inform the efficacy of salvage chemotherapy, the Company believes that the limitations of the Kuhlen *et al*. (2017) study are greater than those of the Jeha *et al*. (2006) study, which the Company maintains is the most appropriate source of efficacy for salvage chemotherapy. Nevertheless, Kuhlen *et al.* (2017) has been included in the model leveraging the parameters that were incorporated in the EAG-version of the company submission model from TA554; as this has been directly leveraged from the EAG model, only the parameters included by the EAG are available in the model (Weibull, log normal and generalised gamma cure models, and all six key functions for non-cure. It should be noted however that the non-cure Gompertz parameters generated in the EAG-version of the company model in TA554 did not and does not generate plausible survival curves). Statistical fit data are also not reported for the cure models.

Section C: Clarification on cost-effectiveness

C1. Priority. CS, Section B.2.3.2, page 38, and Section B.2.8, page 77. CS Section B.2.3.2 states *"All three trials had a very similar study design, ALL patient population and methodology"*, CS Section B.2.8 states *"the median dose received across all three trials was of the same magnitude and therefore this difference was not expected to bias the pooled estimate of efficacy for tisagenlecleucel."* Section B.2.8 concludes that *"Overall, it was considered that any differences between baseline characteristics were minor, and therefore it was considered appropriate to pool the data from all three trials. Furthermore, the eligibility criteria of all three trials match the intended patient population for tisagenlecleucel in UK clinical practice.[2, 5, 6] Therefore, taken together, the pooling of all three trials generates a larger sample size of a group of patients that can be considered, overall, to be representative of the "true" population likely to be treated with tisagenlecleucel in UK clinical practice."* Please clarify why the pooled tisagenlecleucel dataset has not been used in the economic model.

In the original CS (TA544), data were pooled across the tisagenlecleucel trials (ELIANA, ENSIGN and B2101J) to generate a larger sample size of patients and to increase the length of data follow-up.[1] Whilst there were differences noted between the trials in terms of baseline characteristics and methodology, these were considered to be minor and therefore it was considered appropriate to pool the data from all three trials.

As quoted within the text of this question, the pooling of all three trials was also conducted for this submission, and generates a larger sample size of a group of patients that can be considered, overall, to be representative of the "true" population likely to be treated with tisagenlecleucel in UK clinical practice. This text is taken from Section B.2.8 of the CS which describes the patient baseline characteristics from the pooled analysis. Naturally, when considering patient baseline characteristics, then the pooled analysis provides a more complete reflection of the "true" population likely to be treated with tisagenlecleucel in UK clinical practice.

However, when considering the data to be used in the economic model in the current submission, the use of the pooled analysis was not considered appropriate for a number of reasons: a) results of the pooled dataset versus ELIANA alone were considered to be comparable and therefore did not suggest that one dataset should be used over the other and b) use of the pooled dataset resulted in a shorter median follow-up than use of ELIANA alone (48.2 months versus 79.4 months, respectively).[4]

As noted by the EAG in TA554, there were small numbers of patients at risk beyond 18 and 36 months for ENSIGN and B2101J respectively, thereby necessitating longer follow-up to reduce uncertainty on the clinical benefit of tisagenlecleucel.[1] The EAG also noted that a 5-year follow-up would be more indicative of the curative potential of tisagenlecleucel.[1] In the current submission, clinical evidence from ELIANA, ENSIGN and B2101J were presented with longer follow-up durations of 79.4, 31.7 and 47.2 months respectively.[4, 12, 13] However, as noted in B.2.6.3 of the CS, the interpretation of the OS curve in the ENSIGN trial continues to be limited as only eight patients were at risk beyond 24 months.[12] Whilst B2101J has 37 patients at risk beyond 25 months, the patient numbers are low at Month 60 with only 2 patients at risk. In contrast, the ELIANA trial has 25 patients at risk at Month 60 along with a clear plateau emerging from Month 24 with 49 patients at risk.[4]

Considering the long-term data available for a larger patient population at the 5-year follow-up point, the ELIANA trial represents the most appropriate source of evidence that is indicative of the curative potential of tisagenlecleucel, and therefore has been used to inform the economic model. Given the small patient numbers at risk at later timepoints in ENSIGN and B2101J, the pooling of these two trials with ELIANA would not address the key clinical uncertainty of the lack of mature data raised by the Committee and EAG in TA554.[1] Therefore, by only using the ELIANA trial to inform the model, the robustness of clinical evidence informing tisagenlecleucel efficacy is retained and any inherent limitations on the comparability of trials associated with pooling data are averted.

Survival analysis

C2. Priority. CS, Section B.3.3.3, pages 128-150. Please clarify if the EFS data from ELIANA used to inform the economic model include censoring of allo-SCT. Please also clarify why the Kaplan-Meier plot in CS Figure 20 and the KM plot in the economic model (worksheet "Probabilities (Tisagen)", column X) appear to be different. For example, in CS Figure 20 the last observed event occurs at around Month 54, whereas in the economic model it is at around Month 48.

The EFS data used to inform the economic model were obtained from the latest CSR for ELIANA (DCO 17th Nov 2022; presented in Figure 9 in the original CSR)[4] and includes the censoring of allo-SCT.

The EFS data in the economic model have been updated to include censoring for HSCT regardless of later deaths, and a discrepancy in patient numbers has been corrected (see response to Question B15). There is a minimal impact on the updated company base case, as reported in the Appendix.

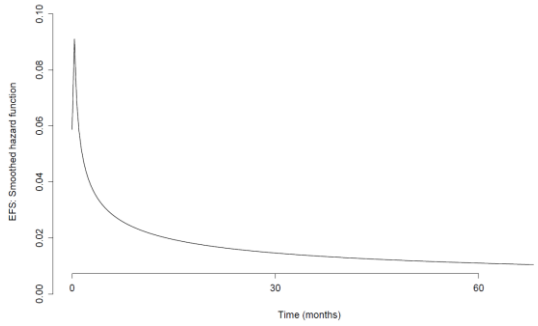
C3. Priority. CS, Section B.3.3.3, pages 128-150. For the pooled dataset, for each of EFS and OS, please provide plots of the empirical/smoothed hazard function. Please also plot the hazard function of the company's base case survival model on top of the empirical and smoothed hazard on these same plots.

Plots of the empirical/smooth hazard function for EFS and OS from the pooled dataset are provided below with the plot of company's base case survival model hazard function provided alongside in Figure 14 and Figure 15

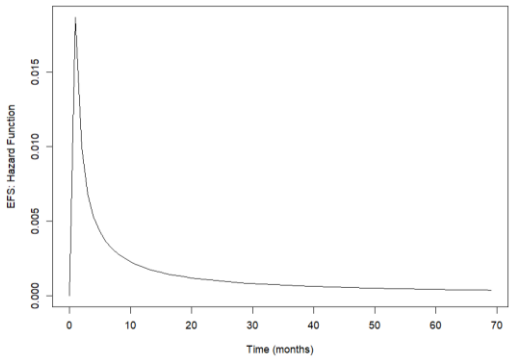
Figure 15. Please note that the company base case hazard function applies only to non-cured patients, as this is what the survival parameters correspond to in a mixture cure model.

Figure 14: Empirical/smoothed hazard function for EFS from the pooled dataset and from the company base case

Pooled dataset



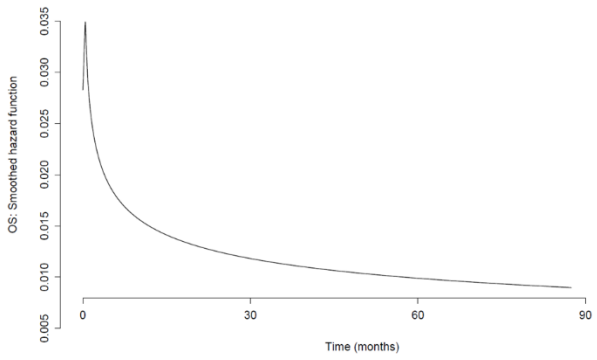
Company base case



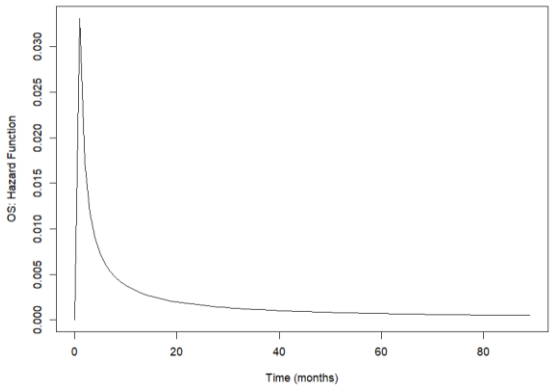
Notes: The company base case survival model is based on a log-logistic distribution and applies to non-cured patients only.
Abbreviations: EFS: event-free survival.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018).[13]

Figure 15: Empirical/smoothed hazard function for OS from the pooled dataset and from the company base case

Pooled dataset



Company base case



Notes: The company base case survival model is based on a log-logistic distribution and applies to non-cured patients only.
Abbreviations: OS: overall survival.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018).[13]

C4. CS, Section B.3.3.3, Table 36, page 133 and Table 44, page 144. The company's base case mixture-cure models suggest cure fractions of 34.9% for EFS and 42.4% for OS in the tisagenlecleucel group. Please comment on the clinical plausibility of applying a higher fraction for OS than EFS.

EFS in the ELIANA trial was defined as the time from treatment to the *earliest* of death, relapse or treatment failure (no response in the study or discontinuation due to AEs, lack of efficacy, or new anticancer therapy). Theoretically, the cure rate estimated from the OS mixture cure model refers to the proportion of patients who do not have disease-related death, whereas the cure rate estimated from EFS mixture cure model refers to the proportion of patients who do not have disease-related events or death. As such, they are not expected to be exactly the same. Clinically, they should be similar or comparable as those who die from disease are most likely to go through relapse or treatment failure first.

Whilst the base case cure fractions are not identical, these can be considered comparable. Nevertheless, as the shape of the EFS curve from the tisagenlecleucel trials is less smooth compared to OS, in general, all the parametric functions and mixture cure models do not fit the EFS curve as well as the OS curve. As such, the fitting for the EFS curve may be less stable, contributing to the variation observed in the cure fractions for the EFS curves.

C5. Priority. CS, Section B.3.3.3, page 142. The economic model applies a standardised mortality ratio (SMR) of 4.0, based on clinical opinion. This is considerably lower than the SMR used in TA554. Please provide further information about how this updated estimate was obtained – how many clinical experts were asked and what question was asked?

The SMR of 4.0 was obtained based on clinical feedback sought as part of this appraisal. This recent feedback therefore better reflects the expected long-term survival of patients who have received CAR-T therapy compared with the experience and knowledge available at the time of the original submission. The clinical validation report has been provided as part of the reference pack in this submission ("Clinical Validation Report_2023"), with further details on the clinical validation exercise provided in this report and Section B.3.3.3 of the CS.[6] A total of three UK clinical experts were consulted whom are existing or former NHS Consultant Haematologists and were all experienced in the treatment of r/r B-cell ALL along with clinical experience of using tisagenlecleucel.

Prior to the respective clinical validation calls, a pre-read questionnaire was provided to the experts to provide estimates of SMR for patients who were considered to be "cured", relative to the general population. The clinical experts were presented with details on the SMR value of 9.05 applied in TA554 which was based on MacArthur *et al. (2007)* and other alternative SMRs (15.20 and 15.10–20.90 [age-dependent]) which were explored as scenario analyses. [1, 30] Experts were also presented summarised findings from the Committee meeting for brexucabtagene autoleucel for r/r B-cell ALL in people aged 26 years and over (TA893) whereby the SMR for patients was anticipated to lie between the company base-case (1.09, in line with a previous appraisal of an adult population in DLBCL) and the EAG-preferred base-case (4.00, based on survival 5 years after hematopoietic cell transplantation).[31] Clinicians were then asked *"Considering the data provided, and the understanding that some patients would be cured after treatment, please provide lower, upper and most likely SMR estimates for paediatric ALL patients considered to be "cured", relative to the general population"*. The clinician estimates, as presented in Table 4 of the clinical validation report, are presented below in Table 19. The average clinician estimate of 3.7 therefore, informed the SMR of 4 used in the base case for the current appraisal in favour of literature values previously used in TA554.

Finally, the broader context of CAR-T therapies in UK clinical practice is noteworthy. At the time of the initial appraisal (TA554), CAR-T represented a step-change in potential treatment for various cancers. Over the last 5 years, clinicians have gained experience using CAR-T therapies and more recent NICE appraisals of CAR-Ts have used SMRs for long-term survival much lower than that reported in TA554.[1] TA872 (axicabtagene ciloleucel in diffuse large B-cell lymphoma [DLBCL] 3L+) used an SMR of 1.09, whilst the Committee in TA893 (brexucabtagene autoleucel in r/r B-cell ALL) favoured a SMR of 3.[31, 32] In the most recent CAR-T appraisal, TA895 (axicabtagene ciloleucel in diffuse large B-cell lymphoma [DLBCL] 2L+), the same SMR as in TA872 (1.09) was used.[32, 33] In addition to being in line with clinical expert opinion, the SMR of 4 therefore represents a conservative estimate based on most recently accepted assumptions in CAR-T appraisals.

Table 19: Clinician estimates of SMR in patients considered cured

Clinician responses	Estimated SMR		
	Lower plausible	Most likely	Upper plausible
Expert 1	2.0	4.0	10.0
Expert 2	1.5	3.0	6.0
Expert 3	3.0	4.0	6.0
Average	2.2	3.7	7.3

Taken from Table 4 of Clinical Validation Report 2023.[6]
Abbreviations: SMR: standardised mortality rate.
Source: Novartis Data on File (2023; Clinical Validation Report).[6]

C6. Priority. CS, Section B.3.3.3, Table 37, page 135 and Table 45, page 146. These tables provide Kaplan-Meier survival estimates, survival model predictions and clinicians' estimates of EFS and OS at 1, 2, 5, 10 and 20 years for patients receiving tisagenlecleucel.

a) Please clarify if the survival model predictions shown in this table include the SMR.

As noted in Section B.3.3.3 of the CS and in response to Question C16 below, the SMR-adjusted general population mortality is only used to bound the modelled OS rather than directly influence the mortality applied to the 'cured' proportion of patients. The 'model estimates' shown in Table 37 and Table 45 therefore do not include the 'capping' of survival by SMR-adjusted general population mortality, however, this is also not expected to occur for any of the presented time points in this table (up to 20 years) and therefore, if this capping was applied, there would be no impact on the numbers presented in the table.

b) Please provide each of the clinicians' individual predictions for EFS and OS (highest, lowest and most likely), rather than the average of their values.

Individual clinician estimates are provided in Appendix A of the validation exercise report included in the reference pack provided alongside the CS (please refer to the Word file named "Clinical Validation Report_2023").[6]

c) Please clarify if the clinicians' estimates relate specifically to those patients who were successfully infused with tisagenlecleucel.

Yes, clinicians were presented with efficacy data from ELIANA for patients successfully infused with tisagenlecleucel, and were subsequently asked to provide estimates based on these data and their experience using tisagenlecleucel in UK clinical practice, assuming successful infusion.

d) For OS, the log-normal model appears to provide a closer approximation to the clinicians' expected OS compared with the company's preferred log-logistic model. The difference in relative statistical fit between these models is negligible. Please clarify why the log-normal OS model was not selected for use in the base case analysis.

Whilst the Company agree that the log-normal model appears more closely aligned with clinician estimates of OS at certain timepoints (mainly year 10 and year 20), the log-normal model's predicted cure fraction (33.2%) is poorly aligned with clinicians' predictions (40.0%), as compared with the cure fraction predicted by the log-logistic model (42.4%).[6] Furthermore, the log-logistic and exponential model curves were

explicitly noted by clinicians as most closely aligning with their expectations of tisagenlecleucel efficacy in terms of OS. The log-normal model is therefore likely to underestimate long-term ALL survivorship, and was therefore not considered appropriate for inclusion in the Company base case, in favour of the log-logistic model. The exponential model was used in a scenario analysis.

e) Please comment on whether there any long-term data are available for other CAR-Ts in similar ALL populations.

As per the clinical SLR performed by the Company which screened for studies evaluating CAR-T cell therapies in the patient population of interest, no publications were found which evaluated other CAR-T therapies in use for the treatment of paediatric and young adult patients aged up to 25 years with r/r B-cell ALL.

f) Please clarify if a similar clinical validation/model selection exercise was conducted for either comparator (blinatumomab or FLAG-IDA). If not, why not?

In the absence of EFS data for blinatumomab or FLAG-IDA, only the OS extrapolations for each comparator were validated. OS extrapolations using the models previously preferred by the Company, EAG and Committee in TA554 were shown to clinicians, who were asked to comment on their respective validity.[1] Clinicians were additionally asked to provide estimates of the proportion of patients they would expect to achieve long-term survival. As noted in the submission, it is likely that clinicians' estimates of subsequent SCT were significantly higher than those reported in von Stackelberg *et al.* (2016)[10] and Jeha *et al.* (2006),[11] which may have biased their estimates of long-term survival.

Whilst clinicians did not indicate a particular preference for any given curve, they generally agreed that the presented curves were clinically plausible and reflective of outcomes seen in clinical practice. Statistical fit and clinicians' predictions of long-term survival (accounting for higher rates of SCT) were therefore used to inform the base case extrapolation.

Given the survival models derived from von Stackelberg *et al.* (2016)[10] and Jeha *et al.* (2006)[11] for blinatumomab and FLAG-IDA respectively, had previously been validated, it was not deemed necessary to elicit survival outcomes for the comparators, as was done with tisagenlecleucel, now informed by more mature ELIANA data. The full results of the validation exercise conducted for the comparators can be found in the report provided in the reference pack submitted alongside the CS.

C7. CS, Section B.3.3.3, page 147. The text states *"It was assumed that the cumulative hazard function for EFS would be proportional to the cumulative hazard function for OS. The ratio between EFS and OS was modelled based on data from the UK ALL study, a study of mitoxantrone in children with a first relapse of ALL."*

a) Please justify the appropriateness of this assumption.

The absence of EFS data from the sources of efficacy for comparators necessitated EFS to be derived from the OS data available. This relationship is justified on the basis that EFS is highly correlated to OS, with multiple studies reporting strong correlation between the two outcomes in blood cancers.[34] As noted in the CS, this approach has previously been taken in the NICE mock technology appraisal for CAR-T therapies, and was accepted by both the EAG and Committee as appropriate.[1, 35]

It should be noted that both EFS and OS data for salvage chemotherapy are available from the Kuhlen *et al*. (2017) study, which the Company have added to the model following the request from the EAG in Question B34. In the scenario where OS for salvage chemotherapy is informed by Kuhlen *et al.* (2017), the choice of EFS data extrapolated from Kuhlen *et al*. (2017) or derived from OS data, as done in the Company approach, impacts the ICER only marginally, indicating the assumption of a proportional relationship between EFS and OS to be robust for decision-making.

b) Please clarify how the ratio was extracted from the UK ALL study.

As the UK ALL study only reported progression-free survival (PFS) rather than EFS, PFS was used as proxy for EFS. The PFS and OS Kaplan-Meier curves reported for mitoxantrone in the UK ALL study were digitised to obtain PFS and OS survival estimates at years 1, 2, 3 and 4. These were subsequently used to estimate cumulative hazard functions of OS vs PFS at these timepoints, by logging the OS and PFS estimates at each year and calculating a ratio (the resultant HRs are shown in cells D23:D26 of the 'Parameter Estimates (EFS)' sheet in the model). These were then averaged to obtain the ratio of cumulative hazard functions between OS and EFS of 0.83 used for both comparators in the model.

c) Please clarify whether the data from the Idarubicin arm were used to calculate the ratio between EFS and OS.

No, only data from the mitoxantrone arm were used to derive the HR between EFS and OS.

d) Please also clarify whether data from the tisagenlecleucel studies (ELIANA, ENSIGN, B210J) suggest the same ratio.

A similar derivation from the EFS and OS survival data for ELIANA included in the model suggest a HR of ~0.67. However, the relationship between EFS and OS of tisagenlecleucel is unlikely to be comparable to that of FLAG-IDA or blinatumomab, given the greatly different mechanism of action of tisagenlecleucel. As noted in response to Question B2 above, tisagenlecleucel is prescribed with the intent to achieve long-lasting survival, whilst blinatumomab and FLAG-IDA are prescribed as bridging therapy to allo-SCT.

Costs

C8. Priority. CS, Section B.1.2, Table 3, page 22. Please confirm that in the cases where a patient is not successfully infused with tisagenlecleucel, either due to manufacturer error or patient disease progression/death, the company will bear the cost.

The Company confirms that in cases where a patient is not successfully infused with tisagenlecleucel, either due to manufacturer error or patient disease progression/ death, the company will bear the cost.

C9. CS, Section 3.5.1, Tables 53 and 54, pages 168-169. The cost calculations for blinatumomab assume that patients have a BSA of 1.17m^2 whereas the calculations for FLAG-IDA assume a BSA of 1.25m^2. Please clarify why different BSAs have been assumed.

As detailed in Section B.3.5.1 of the CS, the cost calculations for blinatumomab account for the different dosing regimens by age. The blinatumomab dosing for patients under 18 years was based on dosing schedule used in the study by von Stackelberg *et al.* (2016), which is BSA-dependent.[10] Given this dosing was explicitly for patients under 18, the mean BSA of patients under 18 years in the ELIANA trial was calculated, resulting in a BSA of 1.17 m^2.[10] The blinatumomab dose for patients over 18 years was based on the blinatumomab SmPC, where the average dose required per infusion for the adult population was independent of the patient BSA.

The cost calculations and relevant dosing regimen for FLAG-IDA are independent of patient age. Therefore the dosing calculation is based on the average BSA of all patients in the ELIANA trial, which is 1.25 m^2.[4]

Therefore, different BSAs have been assumed for the calculation of each dosing regimen, dependent on whether the dosing regimen is relevant for the full population (in the case of FLAG-IDA) or a subset of the population (in the case of the blinatumomab regimen for patients < 18 years).

C10. CS, Section B.3.5.1, Table 53, page 168. Please clarify how the distribution of patients receiving blinatumomab per cycle has been calculated (96% in cycle 1 and 31% in cycle 2).

The percentage of patients receiving each cycle of blinatumomab was based on treatment exposure data from Figure 2 in von Stackelberg *et al.* (2016) and, in the absence of alternative data, was assumed to be the same for patients receiving either dose (< 18 years or ≥ 18 years).[10]

For cycle 1, the number of patients who received blinatumomab is 67 (Phase I, n=26; Phase II, n=41) compared to a total number of patients who started treatment of 70 (Phase I, n=26; Phase II, n=44). Therefore, the proportion of patients receiving blinatumomab in cycle 1 is conservatively assumed to be 96% (n=67/70). Similarly, the proportion of patients receiving blinatumomab in cycle 2 (31%) is derived as the sum of patients who received blinatumomab in cycle 2 (Phase 1: n=11; Phase 2: n=11) divided by the total sum of patients who started blinatumomab treatment (n=22/70).

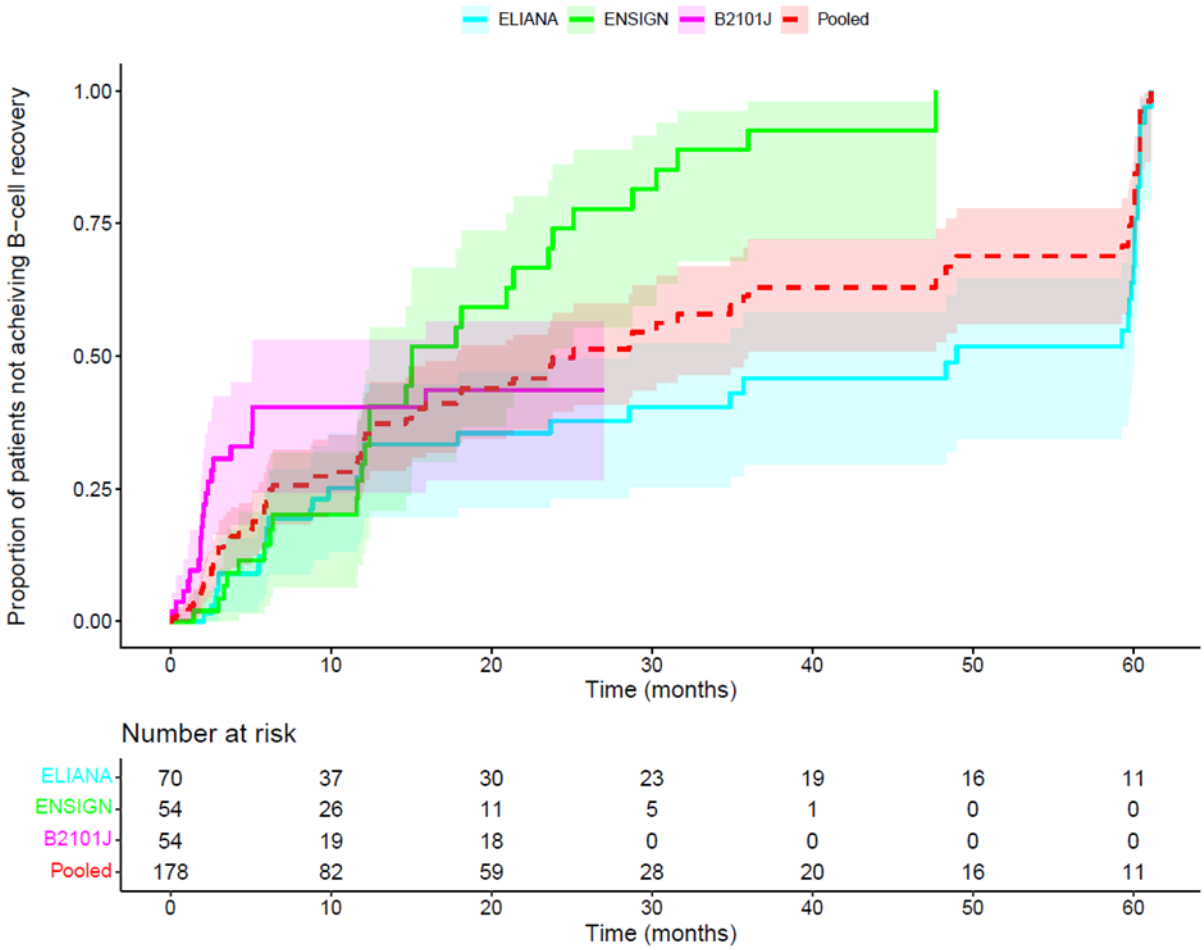
C11. Priority. CS, Section B.3.5.3, page 176. Please provide a plot of time to B-cell recovery from ELIANA, ENSIGN, B2101J and the pooled dataset, and provide

updated estimates of the proportion of patients with hypogammaglobulinaemia from each of these studies.

The plot for time to B-cell recovery is presented below for ELIANA, ENSIGN, B2101J and the pooled dataset. Please note that the numbers of patients at risk for each trial at the beginning of the analysis period is lower than the total number of patients, as B-cell recovery was only analysed for patients who achieved remission (CR/CRi).

The proportion of patients with hypogammaglobulinaemia for each study is provided in the list of AEs provided in response to Question B26.

Figure 16: Time to B-cell recovery in ELIANA, ENSIGN, B2101J and the pooled dataset



Abbreviations: CSR: clinical study report.
Source: ELIANA CSR (17th Nov 2022);[4] ENSIGN (24th May 2019);[12] B2101J (7th May 2018).[13]

C12. CS, Section B.3.5.3, page 176. Please clarify whether the proportion of patients with hypogammaglobulinaemia and the median duration of IVIg applied in the model reflects the 2017 DCO of ELIANA (as indicated in the model, worksheet "AE Cost Inputs", cell F28) or the 2022 DCO of ELIANA (as indicated in the CS, Section B.3.5.3).

The 73.3% intended to represent the proportion of patients with hypogammaglobulinaemia was incorrectly retained from the original Company submission (TA554). The original value of 73.3% was the proportion of patients receiving IVIg replacement therapy as reported in the ELIANA CSR (DCO 25th April 2017).[36]. However, based on feedback from the EAG that indicated only patients with hypogammaglobulinaemia would receive IVIg treatment for B-cell aplasia, this input was reconsidered. As such, this value should reflect the proportion of patients with hypogammaglobulinaemia (all-grade) as observed in the 17th November 2022 DCO of ELIANA (40.5%).[4] The Company apologises for this error, and has updated the base case accordingly, the results of which can be found in the Appendix.

Executable model

C13. Executable model, worksheet "Life Table", cells G21:G120. The formulae in this cell range assume that the proportionate split of men and women remains constant at every age, yet the life table probabilities indicate that men and women have different age-specific risks of death. Both of these cannot simultaneously be true. Please amend the model to use a weighted survival model, based on separate survival models for men and women, with the weighting applied at baseline.

The Company are aware of the simplifying assumption to assume that the proportionate split of men and women remains constant at every age, which is commonplace in economic models.

Nevertheless, as requested by the EAG, the model has been updated to include a weighted survival model based on the separate survival estimates for males and females. The impact on the cost-effectiveness results are very minimal (change to base case ICER of ~£[redacted] in both arms); all updates to the Company base case are summarised in the Appendix.

C14. Executable model, all three model trace worksheets, column H. The formulae in these cells apply the maximum of the mortality risk from the parametric survival model and the life table estimate. However, the life table mortality estimate for 12 year olds (in the first year of the model) is applied for 11 cycles rather than 12. Please confirm that this is an error and correct it in an updated version of the model.

The Company apologies for this error in the model and have corrected the calculations to ensure that the mortality risk associated with the age during the previous cycle is applied to derive the relevant OS for the next cycle (and as such, the life table mortality estimate for 12 year olds is applied for 12 cycles, rather than 11 cycles).

The impact on the cost-effectiveness results are very minimal (change to base case ICER of ~£[redacted] versus each comparator); all updates to the Company base case are summarised in the Appendix.

C15. Executable model, all three model trace worksheets, column N. The formulae in these cells use a =MIN() function to constrain the cumulative probability of EFS by

the cumulative probability of OS in each cycle. Given that EFS is a composite endpoint, this means that the model is assuming that the rate of relapse or death in ALL is lower than the rate of death in this same population. Please confirm that this is an error and correct it in an updated version of the model. If this was not an error, please justify this assumption.

Given EFS is a composite endpoint that includes OS events, it should not be possible for the cumulative probability of EFS to exceed that of OS, and therefore, the =MIN() function is used to prevent this from occurring. If this constraint was removed, towards the end of the model time horizon (e.g. age 63 in the tisagenlecleucel arm in the Company base case) the modelled EFS and OS curves would cross. It should be noted that this constraint is never 'activated' for the salvage chemotherapy comparator, and only at age 69 when there are ~5% of patients alive for the blinatumomab comparator. The Company would also like to highlight that this approach is as per the original Company submission (TA554).[1]

C16. Executable model, worksheet "Consolidated Probabilities", column N. These formulae refer to the life table mortality risks which exclude the assumed SMR for ALL. Please confirm that this is an error and correct it in an updated version of the model.

As noted in Section B.3.3.3 of the CS, the SMR is only used to ensure that the modelled OS extrapolation does not exceed expected survival for long-term ALL survivors (general population mortality with the SMR applied). This was applied by bounding the OS profile by the SMR-adjusted general population mortality, as applied in column H in all three trace worksheets. It is therefore not an error in the model to not apply the SMR in Column N on the Consolidated Probabilities worksheet as this is meant to represent the survival of the general population before being applied in the cure models. The Company would also like to highlight that this approach is consistent with that taken in the original Company submission (TA554).[1]

C17. Executable model, all three trace worksheets, cells AP12:AP23. Please clarify why the disutility for allo-SCT are not multiplied by the model trace?

The disutility associated with allo-SCT applied in the traces (column AP) has been adjusted by the proportion of patients who receive allo-SCT by treatment arm in the 'Subsequent SCT' worksheet (cells E34:H36). It is further assumed that all patients who undergo allo-SCT live for at least 12 months after treatment and incur the associated disutility for the same time period. This simplifying assumption is made because the progression and survival of individual patients receiving allo-SCT is not explicitly modelled. Given this, no further multiplications are required to derive the disutility associated with allo-SCT.

C18. Executable model, worksheet "AE Cost Inputs", cell C28 and worksheet "AE Rate Inputs" cell C23. The AE rate inputs sheet suggests a frequency of hypogammaglobulinaemia of 8%, whereas the AE cost inputs sheet suggests that

73% of patients received IVIg. Please clarify why there is a difference between these two values? Why is hypogammaglobulinaemia included in both the short and long-term costs?

The frequency of hypogammaglobulinaemia in the short-term (8% as presented in the AE rate inputs sheet) is specific to grade 3 or 4 AEs and it has been included within the calculation of AE costs based on the AE inclusion rule criteria, i.e., any grade 3 or 4 AEs regardless of study-drug relationship that occurred in ≥5% of patients.

C19. Priority. CS, Section B.3.9, Table 68, page 190 and Section B.3.10.1, Table 72, page 191. Please explain why the QALYs estimated using the probabilistic model are notably different from the deterministic results.

The Company does not believe the QALYs estimated using the probabilistic model are notably different from the deterministic model, with a difference of 0.12-0.19 QALYs dependent on the comparator. Given the variation in the 95% CIs of the sampled health state utility values (EFS: 0.91 [95% CI 0.85,0.97] and PD: 0.75 [95% CI 0.69, 0.80]) this level of variation is not unexpected. As can be seen from the scatter plots (Figure 37 and Figure 44 in the CS) there is a correlation between incremental costs and incremental QALYs, showing balanced sampling of parameters. Furthermore, the convergence plots within the CS show convergence of the probabilistic results from 1000 simulations, with results similar to the deterministic.

However, the Company acknowledges there is inherent additional uncertainty with the probabilistic model, as not all inputs that are expected to be correlated (e.g. health state utilities, efficacy and safety) are reflected as such in the model, due to data limitations. Furthermore, in the absence of published measures of uncertainty (e.g. standard errors), these have been assumed for some inputs (e.g. costs).

Section D: Requests for additional data and analysis

D1. Priority. Please provide Kaplan-Meier summary data for ELIANA, ENSIGN, B2101J and the pooled dataset for EFS and OS, without censoring for allo-SCT, including N at risk (see example table below). Each row should represent the time at which a new event occurs.

Table 1: Example Kaplan-Meier summary

Time of event (months)	No. events	N at risk	Survival probabilities, S(t)
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX

Kaplan-Meier summary data for OS and EFS, with censoring for allo-SCT for ELIANA, ENSIGN, B2101J and the pooled dataset is provided in the reference pack accompanying this response document, based on the example table provided. Please note that as no censoring was ever included for OS, this should be identical to that already presented in the CS (e.g. Figure 21 in the CS).

D2. Priority. Please re-fit all standard parametric survival models and mixture-cure models parametric survival models to the full pooled dataset including ELIANA, ENSIGN, B2101J for EFS and OS, as was done in TA554. As part of this exercise, please also fit cubic spline models to the pooled data (including models with up to 3 knots, fitted on the hazard, odds and normal scales). Please update the economic model to include functionality to select any of these parametric survival models for each treatment group and each endpoint.

Standard parametric survival models and mixture-cure models have been fitted to the full pooled dataset including ELIANA, ENSIGN, B2101J for EFS and OS, as done in the original CS (TA554).[1] This functionality has been included in the updated Company economic model provided alongside this response document.

In the original CS (TA554),[1] flexible models (i.e., spline models) were explored for extrapolation, given that they allow for the characterisation of more complex hazard functions. Spline models were seen to be unable to capture the observed plateau and the expected continuation of this plateau in the longer-term for tisagenlecleucel, for both EFS and OS. Furthermore, spline models were not explored for the mixture cure model approach given the lack of an established approach for incorporating these model types. It was also highlighted in the original submission that splines, while producing a strong statistical fit to observed Kaplan-Meier data, can produce clinically unrealistic extrapolations in the long-term and fail to reflect the clinical mechanisms underlying the observed hazard function.[37] The EAG and Committee thus accepted the mixture cure model approach for all comparators and this has been reflected in the CS. Therefore, spline models have not been incorporated in the model.

D3. Priority. Please update the economic model to include functionality to include the MAIC-adjusted tisagenlecleucel survival functions based on the pooled dataset. Please also include the adjustment for EFS as well as OS.

MAIC results for the pooled dataset were presented in Appendix D of the CS. As discussed in Section 2.9 of the CS, the matched and unmatched data were highly similar for both comparisons; an observation that is true for both the ELIANA alone and pooled dataset. In all comparisons, the 95% confidence intervals of the matched and unmatched tisagenlecleucel curves overlap substantially, indicating that differences between the matched and unmatched curves may reflect uncertainty inherent in the sample estimates rather than a true difference in efficacy. Given the lack of meaningful differences in efficacy estimates when adjusting for population differences across the intervention and comparator trials, unadjusted data were used

in the economic analysis, which is expected to have a negligible impact on model results while being able to retain the largest sample sizes to inform efficacy outcomes in the model.

However, as requested by the EAG, the functionality for MAIC-adjusted tisagenlecleucel survival functions based on the pooled data has been included in the updated Company economic model provided alongside the response document. As there was no MAIC conducted for EFS (in the absence of any appropriate EFS data for comparators), this has been included for OS only.

D4. Priority. Please update the economic model to include pooled AE frequency data for ELIANA, ENSIGN and B2101J.

The functionality for pooled AE frequency data has been included in the updated Company economic model provided alongside the response document. Pooled AEs were included according to the original AE inclusion rule, where AEs are only modelled if they have >5% incidence in at least one of the treatment arms; incidence is based on Table 11. The company would like to highlight that due to time constraints, the two grade 3/4 AEs which now have greater than 5% incidence in the pooled tisagenlecleucel data which previously were not included in the model, headache and haemoglobin decreased, have not been added into the model.

D5. Please also correct the errors identified in Questions C13-C18 within the updated version of the model.

Please refer to the responses provided to each question; where necessary, updates have been made to the economic model and any questions that have resulted in updates to the Company base case are reflected within the updated Company base case results presented in the Appendix.

References

1. National Institute for Health and Care Excellence. Committee Papers: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. Available at: https://www.nice.org.uk/guidance/ta554/evidence/committee-papers-pdf-6653240173 [Last accessed: 4 May 2023].
2. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood. 2010;116:4099-4102.
3. Lanza F, Maffini E, Rondoni M, et al. CD22 Expression in B-Cell Acute Lymphoblastic Leukemia: Biological Significance and Implications for Inotuzumab Therapy in Adults. Cancers (Basel). 2020;12:303.
4. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (17th November 2022 data cut-off). Data on File. 2023.
5. NHS England. Tisagenlecleucel for treating relapsed or refractory Philadelphia negative and positive B-cell acute lymphoblastic leukaemia in people aged 25 years and under – data review, 2023.
6. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2023.
7. European Medicines Agency. Kymriah (tisagenlecleucel). An overview of kymriah and why it is authorised in the EU. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah [Last accessed: 14 April 2023].
8. European Medicines Agency. Summary of product characteristics (SmPC): BESPONSA (Inotuzumab ozogamicin). Available at: https://www.ema.europa.eu/en/documents/product-information/besponsa-epar-product-information_en.pdf [Last accessed: 4 May 2023].
9. Children's Cancer and Leukaemia Group. UK Acute Lymphoblastic Leukaemia (UKALL) 2019 Interim Guidelines. Available at: https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/UKALL_2019_Interim_Guidance_Final.pdf [Last accessed: 4 May 2023]. 2019.
10. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34:4381-4389.
11. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol. 2006;24:1917-23.
12. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter study to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (24th May 2019 data cut-off). Data on File. 2019.
13. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Subjects with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (7th May 2018 data cut-off). Data on File. 2019.

14. European Medicines Agency. Kymriah (tisagenlecleucel). Summary of Product Characteristics (SmPC). Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf [Last accessed: 14 April 2023].
15. Novartis Pharmaceuticals Ltd. ELIANA, ENSIGN and B2101J analyses. Data on File. 2023.
16. National Institute for Health and Care Excellence. Committee Papers: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia [TA450]. Available at: https://www.nice.org.uk/guidance/ta450/documents/committee-papers [Last accessed: 30 June 2023].
17. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (13th April 2018 data cut-off). Data on File. 2018.
18. Grupp SA, Maude SL, Rives S, et al. Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: Updated Analysis of the ELIANA Clinical Trial. Biol Blood Marrow Transplant. 2019;25:S126-127.
19. Laetsch TW, Maude SL, Rives S, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. J Clin Oncol. 2022;41:1664-1669.
20. Grupp SA MS, Rives S, Baruchel A, Boyer MW, Bittencourt H, Bader P, Büchner J, Laetsch TW, Stefanski H, Myers GD, Qayed M, Pulsipher, MA, De Moerloose B, Yanik GA, Davis KL, Martin PL Nemecek ER, Peters C, Hiramatsu H. Updated Analysis of the Efficacy and Safety of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory (r/r) Acute Lymphoblastic Leukemia. Blood. 2018;132:895-895.
21. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (17th November 2022 data cut-off). Data on File. 2023.
22. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (31st December 2017 data cut-off). Data on File. 2017.
23. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Clinical Study Report (30th January 2017 data cut-off). Data on File. 2017.
24. European Medicines Agency (EMA). Kymriah: EPAR public assessment report update. Available at: https://www.ema.europa.eu/en/documents/variation-report/kymriah-h-c-4090-p46-011-epar-assessment-report_en.pdf. [Last accessed: 1 June 2023]. 2020.
25. Gore L, Locatelli F, Zugmaier G, et al. Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Blood Cancer J. 2018;8:80.

26. Locatelli F, Zugmaier G, Rizzari C, et al. Improved survival and MRD remission with blinatumomab vs. chemotherapy in children with first high-risk relapse B-ALL. Leukemia. 2022;37:222-225.
27. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-847.
28. Phillippo D, Ades T, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available at: https://research-information.bris.ac.uk/ws/portalfiles/portal/94868463/Population_adjustment_TSD_FINAL.pdf [Last accessed: 1 June 2023].
29. Kuhlen M, Willasch AM, Dalle JH, et al. Outcome of relapse after allogeneic HSCT in children with ALL enrolled in the ALL-SCT 2003/2007 trial. Br J Haematol. 2018;180:82-89.
30. MacArthur AC, Spinelli JJ, Rogers PC, et al. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. Pediatr Blood Cancer. 2007;48:460-7.
31. National Institute for Health and Care Excellence. TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. Available at: https://www.nice.org.uk/guidance/ta893. [Last accessed: 21 June 2023].
32. National Institute for Health and Care Excellence. TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Technology appraisal guidance. Available at: https://www.nice.org.uk/guidance/ta872. [Last accessed: 1 August 2023]. 2023.
33. National Institute for Health and Care Excellence. TA895: Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy. Technology appraisal guidance. Available at: https://www.nice.org.uk/guidance/ta895. [Last accessed: 1 August 2023]. 2023.
34. Norsworthy KJ, Gao X, Ko CW, et al. Response Rate, Event-Free Survival, and Overall Survival in Newly Diagnosed Acute Myeloid Leukemia: US Food and Drug Administration Trial-Level and Patient-Level Analyses. J Clin Oncol. 2022;40:847–754.
35. Hettle R, Corbett M, Hinde S, et al. The Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: An Exploration of Methods for Review, Economic Evaluation and Appraisal. Health Technol Assess. 2017;21:1-204.
36. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (25th April 2017 data cut-off). Data on File. 2017.
37. Huang M, Latimer NR, Zhang Y, et al. Estimating the Long-Term Outcomes Associated With Immuno-Oncology Therapies : Challenges and Approaches for Overall Survival Extrapolations, 2018.

Appendix

Updated Company base case

Table 20: Updated cumulative deterministic results based on corrections applied as per Questions C12, C13 and C14 (tisagenlecleucel list price; no severity modifier applied)

#	Scenario*	Versus blinatumomab				Versus salvage chemotherapy			
		Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
0	Base case	[redacted]	7.13	[redacted]	[redacted]	[redacted]	8.18	[redacted]	[redacted]
1	B15/C2: Updated EFS and OS to use n=79 and n=200 populations, as well as updating EFS HSCT censoring definition	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]
2	1 + C12: Proportion of patients with all grade hypogammaglobulinaemia	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]
3	2 + C13: Weighted survival model	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]
4	3 + C14. Correction of error in mortality risk calculation	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life year
Footnote: *Scenarios applied cumulatively

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]

Clarification questions

November 2023

File name	Version	Contains confidential information	Date
ID6290 Tisagenlecleucel clarification letter_additional questions	V0.3	No	28/11/2023

Section A: Additional Questions

A1. In response to clarification question C11 (Figure 16), the company has provided KM plots of time to B-cell recovery. According to the company's submission (page 176), the treatment duration for IVIg is 11.4 months, which is stated to be based on the median time to B-cell recovery. However, looking at the plots provided in Figure 16 of clarification response C11, median time to B-cell recovery seems to be much longer than 11.4 months. Can the company explain?

As highlighted by the EAG, the median time to B-cell recovery as reported in the 17th November 2022 DCO of ELIANA is 38.6 months, which is longer than the estimate used for treatment duration for IVIg in the Company base case (11.4 months). However, based on clinical feedback sought as part of this appraisal, it was confirmed that the estimate for median time to B-cell recovery available in the latest DCO of ELIANA was an overestimation of the average treatment duration for IVIg, as reported in the clinical validation report provided as part of the reference pack in this submission ("Clinical Validation Report_2023").[1] Clinicians were asked to provide an alternative duration for treatment on IVIg, but were unable to comment on this.[1] Given the lack of an alternative estimate for the average duration of IVIg treatment, the estimate for IVIg treatment duration from the original Company submission (TA554; 11.4 months) was retained.[2]

Novartis has just received an addendum to the NHS CDF report, which contains data on real world use of IVIg. According to the addendum "*Of the 121 patients, 57 (47%) patients received IVIg after receiving a single infusion of tisagenlecleucel. The mean duration of therapy was 13.3 months and the median treatment duration for all patients was 17.9 months (95% CI: 7.0, 24.20*)".

Mean IVIg treatment duration in the NHS CDF report (13.3 months) is a little higher than that used in the model (11.4 months), whilst the current base case slightly underestimates the number of patients receiving IVIg following tisagenlecleucel infusion compared to NHS practice (30.38% versus 47%, respectively). Novartis therefore consider that on balance, the figures used in the current base case are reflective of NHS clinical practice.

References

1. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2023.
2. National Institute for Health and Care Excellence. Committee Papers: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. Available at: https://www.nice.org.uk/guidance/ta554/evidence/committee-papers-pdf-6653240173 [Last accessed: 4 May 2023].

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	Anthony Nolan is an independent charity established in 1974. We were the world's first stem cell register and continue to connect people willing to selflessly donate their stem cells with people in need of a stem cell transplant. We also directly support patients and families with information, advice and support around all aspects of stem cell transplant and, increasingly, CAR-T and other cell-based therapies. We provide a telephone helpline and online patient forum, publish information in a variety of formats, provide financial grants and directly fund specialist NHS clinical nurse specialist (CNS) and psychology posts in transplant centres.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]	**Sanofi:** We are due to receive a grant of **£20,000** to support the development of a report highlighting the psychological impact of stem cell transplant and CAR-T on patients and families. Separately we are also due to receive **£4,200** from Sanofi to provide input into the design of a patient survey on the topic of GvHD. **Pfizer:** We received **£300** to attend an advisory board to develop principles of care to inform a Blood Cancer Patient Charter.

If so, please state the name of company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke directly to two parents of children who received Kymriah to treat relapsed or refractory B-cell acute lymphoblastic leukaemia to ask them about their experiences. We also ran an online survey in September 2023 which received six detailed responses from parents/carers of children who received CAR-T to treat B-ALL.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and	Children and young people who develop B-cell acute lymphoblastic leukaemia (B-ALL) are faced with many challenges. Symptoms of the disease can include fatigue, lethargy, breathlessness, changes in behaviour (for example, young children can appear less playful and more sleepy than normal), susceptibility to infection, bleeding and bruising. Often symptoms can come on suddenly or become worse in a short space of time, with around a third of people aged under 50 diagnosed in an emergency setting (data from NHS Digital Routes to Diagnosis publication 2022, unfortunately data on those aged 25 and under is not provided). B-ALL is a fast-developing cancer and so treatment usually begins very soon after diagnosis: *"I went from taking my baby to the doctor because he wasn't quite right to being in an ambulance at 3am being told he might have a stroke."*

social life. Is there any impact on their siblings?	The treatment for the condition is intensive and can span for several years. Typically, children and young people diagnosed with B-ALL are treated with high-dose chemotherapy and steroids. If the B-ALL does not respond to chemotherapy or returns after treatment, patients may receive a targeted immunotherapy and/or a donor stem cell transplant and only if that were not successful would they be offered CAR-T. Treatments such as high-dose chemotherapy can cause many side effects, from short term (e.g. nausea, hair loss, extreme fatigue, severe immunosuppression leading to infections, mucositis) to long term (e.g. loss of fertility, loss of bone density, increased risk of secondary cancers, graft vs host disease (GvHD), organ damage). One parent told us that their child's Clinical Nurse Specialist described their chemotherapy as "*like pouring bleach down my child's throat*". Some patients who develop issues with their mouth or gut due to the chemotherapy need to be fed via "total parenteral nutrition" which is an intravenous feeding line. In very young children, treatment can delay or reverse milestones such as the ability to crawl or walk. Due to their susceptibility to infection patients undergoing a donor stem cell transplant are usually isolated in hospital for weeks to months at a time. Many children and young people experience negative emotional and psychological effects. While in treatment for B-ALL school-age children are often unable to go to school or to socialise with friends or extended family members for long stretches of time due to their vulnerability to infection and needing to spend long periods of time in hospital. Even if treatment can be administered at home, children often need to have "lines" and tubes inserted to administer food and medication, which can make them self-conscious about going swimming or doing other activities. Similarly, young adults with B-ALL often have to leave school, university or work whilst receiving treatment, and are unable to socialise or participate in group activities. The hair loss from high-dose chemotherapy can add to the feelings of self-consciousness and isolation. B-ALL also impacts siblings of patients, particularly those who are still children and teenagers because the intensity of the disease and its treatment means that parents/carers have to focus a lot of their attention on the child with B-ALL:

	"*Our family was broken up again. Her brother missed out on things too, as our focus was on [Patient].”* *“While I stayed at GOSH with my son, I didn't see my younger son at all, I found it emotionally challenging.”* *“It fractured the family – one parent is always away, the other is trying to juggle parenting the rest – it completely changed our family dynamic.”* Older siblings often take on the role of a carer to other siblings, yet this is not necessarily recognised by school, employers or support services. Siblings can experience loneliness due to the reduced contact with their parents and need to protect the unwell sibling from exposure to infection. They can also feel guilt or conflict due to their ability to continue school and other activities whilst their sibling and carer(s) are dealing with the disease. Siblings can also feel anxiety, worry and distress which can last long after the disease.
7. What do carers experience when caring for someone with the condition?	Carers experience many negative emotional, financial and social outcomes. Carers feel anxiety, worry and stress about their child or loved one's health, including whether or not their disease will respond to treatment or return in the future. Carers also told us they feel anger, guilt, fear and helplessness, and exhaustion. Many carers have to leave their jobs, which is particularly challenging for single parents due to the financial strain this puts on them. For those who are parents/carers to young children, the diagnosis and treatment can come as a shock with some parents telling us that they hadn't even been aware that children could develop cancer prior to their own child's diagnosis. Parents and carers can also feel isolated from support networks due to the need to protect their child or loved one from infection and the long spells of time spent in hospital. The below quotes are directly from carers themselves: *“Extreme pressure and anxiety supporting [Patient] through all the treatments over several years. A long lasting impact on the family.”* *“Worry, stress of finances and relationships. Worry for your child and also during covid not being able to share the load as only one parent could stay. Plus the stress of ensuring the care for your child is up to standard”*

	"Anxiety, guilt, fear, helplessness, anger a lot of it." *"It was difficult to watch him struggle. This was particularly hard when he had a reaction to the chemotherapy which left him with some residual brain damage."* *"Constant worry. No time to switch off - organising hospital appointments, travel to them, administering drugs, child entertainment, supervising home education. Cooking and cleaning. Totally exhausting."*
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Current treatments (other than CAR-T) are felt to be extremely challenging in terms of the side effects, many of which can be lifelong, as described above. Because of this, patients and carers feel that the option to receive CAR-T earlier in the treatment pathway (to avoid stem cell transplant wherever possible) would be much preferable.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	There remains a need for treatments with fewer side effects and higher clinical efficacy. Treatments that could enable patients and families to spend less time in hospital would promote a better quality of life.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment?	The patients/carers we heard from had Kymriah offered to them after the disease had relapsed or failed to respond to other types of treatment, such as chemotherapy and/or a stem cell transplant. In some cases, the patient was granted access to Kymriah soon after referral, in others their consultants had to make repeated requests for access before they could start treatment, which took some time.

• Please refer to the MAA re-evaluation patient submission guide	All of the parents we heard from and spoke to were very grateful to have had the opportunity for their children to access CAR-T, including those for whom the treatment was unfortunately not successful. One parent told us that they were initially "*wary of the treatment as there was too much that could go wrong"* but they were then "*glad we had this option as so far everything is going as it should".* Other parents told us: "*We have been overwhelmed by the success of the treatment."* *"CAR-T saved my son's life. I wish we could have had it sooner.*" Often patients and carers we heard from had to travel long distances to access Kymriah, some carers told us they would prefer it if they could access Kymriah closer to their home or not have to stay in hospital as much as they did.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Kymriah is seen as a life-saving treatment that offers hope when all other options have been exhausted. Some of the parents we heard from told us that their children were put on a palliative care pathway before Kymriah became an option. *"So far it's been an extremely positive experience as [Patient) has been in remission for over 1 year. He's been able to return to a more or less normal life with his family and friends and school. He's not had to take further medicines apart from IVIGs which are far less intrusive and impactful compared to chemotherapy."* The parents we heard from unanimously felt that Kymriah offered fewer side effects in comparison to a stem cell transplant or intense chemotherapy which they had received earlier: *"[Patient] had a bone marrow transplant before Kymriah. This was an awful time, she was very poorly after it and me and her dad had to do it in 2 day shifts due to Covid which was awful as there was no one there to support you and it was exhausting with the machines constantly beeping. Kymriah was a lot less scary. She did not lose her appetite and the chemo was less invasive. Plus she got to keep her hair this time."*

	"Much less harsh treatment side effects. Chemotherapy is terrible." *"Donor stem cell was horrific. Spent 4.5 months in hospital. Started in [hospital name] but because of bad GvHD and a botched procedure we had to transfer to [hospital name]. Terrible side effects. Couldn't eat. Terrible painful skin. CAR-T much much better treatment."* The side effects from CAR-T are considerably less intense than from an allogeneic stem cell transplant. Parents, carers and patients would welcome the option to receive Kymriah instead of a stem cell transplant to avoid having to go through those intense side effects and the potential life-long complications. Stem cell transplant can cause chronic graft vs host disease, infertility, secondary cancers, reduced bone density and other significant effects. For very young children these effects may not be apparent until later in life. In addition, allogeneic stem cell transplant depends on the availability of a well matched donor cell source, which can introduce additional worry and uncertainty for patients. Parents and carers feel that Kymriah is a much kinder treatment.
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The disadvantages that were highlighted to us are: • The uncertainty about whether or not Kymriah will work. • The need to travel long distances to access treatment. • The long term effects on immunity.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Kymriah has been transformative in offering people with relapsed or refractory B-ALL, who would otherwise have an incurable disease, a potentially curative option. It has offered unquantifiable hope to patients and families. It offers significantly fewer side effects in comparison to other treatments for B-ALL. It is our opinion that Kymriah should be a fundamental aspect of the treatment pathway for B-ALL and we would favour its availability earlier in the treatment pathway as an alternative to stem cell transplant.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	xxxxxxxxxxxxx
2. Name of organisation	Blood Cancer UK
3. Job title or position	xxxxxxxxxxxxxx
4a. Provide a brief description of the organisation. How many members does it have?	Blood Cancer UK is the UK's biggest blood cancer research charity. We fund research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses who care for people with blood cancer. Blood Cancer UK has ~125 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]	We received £45,380 grant funding from Novartis and £35,000 from Bristol Myers Squibb towards our 'Blood Cancer Action Plan.' *Please note we received £25,000 from Novartis on 25th September 2022 (just missing the 12-month period).*

If so, please state the name of company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Blood Cancer UK has close relationships and maintains regular contact with the haemato-oncology community. We do this through our Healthcare Professional Advisory Panel (HPAP), Nurses Working Group (NWG), our patient ambassador network, our policy panel of members with lived experiences etc. We additionally maintain relationships with many other blood cancer specialists – from research nurses to academic researchers – through our Information and Support, Research, and Policy, Involvement and Volunteering teams. In preparing for this appraisal, we used these established relationships, as well as our social media channels (Twitter, Facebook groups) to reach people with direct experience of both acute lymphoblastic leukaemia and especially those who received the therapy of interest, Kymriah. The relevant group of expert clinicians on leukaemia were consulted for further clinical insight into the condition and the therapy. They also aided our efforts in reaching the target population by referring consenting patients to us who were then extensively interviewed. We have also included information based on our previous conversations with young acute lymphoblastic leukaemia patients. These conversations further built our understanding of the experiences of those affected by the issues of interest for this appraisal.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Acute lymphoblastic leukaemia is the most common cancer in children and young people. Symptoms include, and range from, frequent infections, bleeding from the nose and gums, tiredness, breathlessness, swollen lymph nodes and more. It is a devastating disease that fundamentally turns everything one knows into chaos and uncertainty. Amidst the shock of receiving a diagnosis is the unassailable challenge of grappling with the many streams of information about complex treatments, pathways, and systems whilst simultaneously feeling scared about the path that lies ahead. It can be a very isolating and daunting time for children, young people and their loved ones. Treatment is long, unpleasant, burdensome, and overwhelming. There is a heavy burden borne by patients and carers who experience refractory/relapsing disease in both managing symptoms of the disease, coupled with the treatment toxicities. At a time when socialisation, exploration, personal and educational growth are the norm, being diagnosed with cancer at childhood or adolescence can be profoundly isolating and life changing. Young people described intense feelings of being left behind their peers following diagnosis. A young person described that being diagnosed in their early 20's left them dealing with intense symptoms and a long treatment journey which derailed their plans for further education. Years later, they have never been in employment or pursued their dream degree. Another young person explained that upon receiving the diagnosis, she was told by healthcare professionals her life 'would likely be on hold for two and a half years.' Another young person detailed struggling with the social isolation that came with the diagnosis. She quickly found herself 'enmeshed within an unfamiliar and harsh world whilst watching everyone else carry on as normal.' She further explained the struggles of being an inpatient for extended periods, sharing wards with much older and frailer patients who were 'dying in front of [her]' – memories she still struggles with. Treatments can often bring unwelcome changes in appearance such as hair loss, physical scarring, weight fluctuations. This can negatively impact a young person's psychosocial functions, quality of life, confidence, self-esteem and can increase anxiety about integrating, where possible, into aspects of normal life. Additionally, friendships can become distant. Withdrawal from social activities can lead to delayed or underdeveloped interpersonal skills which impact many other areas of life.

	The changing family dynamics also impact siblings as the family is often hyper focused on the ill child. This can cause siblings to feel isolated, unloved and can therefore decrease their quality of life. This can further contribute to parents' poor mental health as they often grapple with the associated guilt. Childhood and young adult leukaemia is a life altering diagnosis for a lot of patients, even those that do not get the significant long -term side effects.
7. What do carers experience when caring for someone with the condition?	Carers play a significant and crucial role in young patients' disease and treatment journeys. Caring for a very poorly child or loved one can often be physically challenging and mentally exhaustive. Carers often endure the cancer journey alongside the patient and have added responsibilities whilst receiving very little support. They play a holistic role in their positions as carers, managing everything from appointments, transportation, nutritional needs as well as monitoring and responding to the health and wellbeing changes of their loved ones. Oftentimes, families are young and not yet financially established which brings with it many of its own challenges. One patient expert explained how he constantly worried that his siblings felt neglected by their parents' focus on him. His father had to take time off work to care for his very young siblings whilst his mother spent time at the hospital caring for him.
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Although in a young population, there is a high chance of cure, the treatment is intensive and brings with it a high risk of acute and long-term side effects. Treatment is prolonged with the impact of being on oral chemotherapy maintenance for several years. This has huge impacts on children and young people with regards to their long-term health, anxiety about risk of relapse, interruption of study and work and isolation from peers. Additionally, some deal with changes in appearances (e.g., secondary to steroids or to chronic skin graft versus host disease). Risk of treatment-related mortality is significant for those who require allogenic stem cell transplants. The current treatment regime was described by some as the 'longest, most intensive treatment journey that's been heard of.' A consultant explained that prior to Kymriah, patients who relapse at the second line

	are left with only one curative option (normally targeted agents such a Blinatumomab or Inotzumab) followed by an allogeneic haematopoietic stem cell transplant. However, this carries with it a significant risk of transplant-related mortality (10-20% depending on fitness of patient and donor). Additionally, a risk of relapse is still present post haematopoietic stem cell transplant. In this relapsed/refractory setting, alternatives offer 'only the illusion of options.' Where previous treatments have failed, one young person described being told that if Kymriah was not an option, the only other alternative would be a 'second go' at an already trialled and failed stem cell transplant- the difference this time would be for the patient to be 'hit harder.' This understandably triggered worries around her 'now weaker' body's ability to tolerate another invasive round. The other scenario without a CAR-T is palliative care or the hunt for a suitable clinical trial. We have consistently heard haematopoietic stem cell transplants being described as incredibly challenging – both to endure and recover from. One person described it as being the 'hardest thing' she ever had to face. She expressed 'every potential side effect, explained as a possibility, became a materialised reality for me.' The transplant made her lose so much weight, she became a 'shadow of [her] former self.' Although patients are prepared for many hurdles on the road to recovery from treatments, the intensity of the hardship is often never expressed well enough. People with lived experience emphasised that recovery is a very long and slow process. They described it taking at least a year post-transplant to feel 'somewhat normal again'. Another patient explained how the full body radiotherapy she received during stem cell transplant induced early menopause. Although it is now being managed by hormone replacement therapy, she explained it has been 'mentally very tough' to realise, accept and deal with. She also suffers from long term side effects such as avascular necrosis which resulted in her needing hip replacement surgery to restore hip function. She is also still on a waiting list for surgical management of the shoulder issues caused by the treatment she had years ago. A carer described the trauma of witnessing their daughter's transition from a healthy girl to a now 'much tinier, bald, no-eyebrows, no-eyelashes person' who they knew was their daughter inside. The family explained how they could not accept the reality of 'just how weak and poorly' the disease and the current treatments can make someone you love.

9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	Yes. There is a significant unmet need for effective, ideally curative treatments at this line. In the absence of this, there is still a need for treatments with fewer long-term side effects which can also provide durable remissions, where traditional treatments have failed. Patients whose disease fail to respond to more than one line of therapy currently face exceptionally limited options. This is a significant unmet need. This cohort of patients and their carers view the current treatment landscape as suboptimal and 'hopeless.' Kymriah offers patients at this line of treatment a better chance of achieving remission where previous treatments have failed, and options have been exhausted. It is important to note that not all patients will be able to achieve a second remission to allow a haematopoietic stem cell transplant to proceed and others simply may not have a suitable donor. CAR-T may be curative in patients without the need for an allogeneic stem cell transplant. Comparatively, it has no risk of graft versus host disease, significantly lower risk of new comorbidities, improved quality of life and a faster return to work/education than for those patients that have to undergo a transplant. A previous discussion with two parents of young adults who died following treatment for acute leukaemia revealed they were desperate for more lines of treatment or clinical trials to try when standard treatment did not work. However, they wanted this treatment to be less debilitating, and were also concerned about late effects.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	At this relapsed, refractory setting, 'a lot is riding on Kymriah' because patients and carers put all their remaining hopes on the treatment as it is the 'last, real option' for them. One patient described it as being the 'last throw of the dice.' Patients were well prepared by health care professionals of the possible side effects which both contributed to additional anxiety but also a feeling of preparedness. As it is not a treatment that can be administered at home or widely available in small local hospitals closer to patients, accessibility can be unequal and burdensome. Some patients described needing to travel long distances which significantly contributed to their stress. As this patient population is young, some also described feeling out of their depths in a new place whilst embarking on their last chance of a cure. Patients reported staying in accommodations close to the centres for one full month following CAR-T, after being an inpatient for 2 weeks, which wasn't easy but offered them reassurance. Another person who resides close to a CAR-T delivery centre explained travel was not an issue for her at all because of the close proximity to her house but recognised this can cause stress on other patients, especially those who may not have the support of dedicated carers. On accessibility and eligibility, patients explained how bizarre it was to know a handful of people, who did not know them, could 'decide their fate' and whether they should be given 'the right to survive.' Additionally, the patients able to access and receive Kymriah recognised their privilege as they acknowledged there are others who, due to their age, location, fitness level or other circumstances cannot access a potentially curative treatment.

11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The biggest advantage identified by patients and carers is Kymriah's curative potential, especially for those in the relapsed/refractory population facing extremely limited treatment options and where general post-relapse prognosis and survival are poor. This benefit is particularly favourable considering it is a one-time treatment. Even if not curative for all, its ability to achieve remission with a significant duration can greatly improve quality of life for both patients and carers. Kymriah's availability, made possible through the Cancer Drugs Fund, has been described as truly transformative and a substantive advance in shifting childhood and young adult cancer care by both patients, carers, and clinicians. It is not a small victory that Kymriah is able to offer an entirely game changing, life-altering option to people who previously faced poor prognosis and would have otherwise likely engaged in palliative conversations. One patient explained the significance of not losing her hair - a worrying concern for her given the use of chemotherapy for CAR-T. The lower dose didn't cause hair loss. This, she explained, meant 'I could see myself in the mirror everyday rather than the shadow of my former self I had seen with previous treatments.' Another advantage highlighted by the same patient was that although she experienced different side effects such as fever, low blood pressure and headache, it was all controlled on the ward and she didn't require intensive care at any point. She added she was able to independently engage with the day without assistance from nurses and reported feeling 'relatively well in the hospital itself.' She was doing 'bits and bobs of yoga' which she explained could never have been done during her stem cell transplant journey. She was also only an inpatient for 2 weeks as opposed to the 9 weeks for her previous stem cell transplant and described feeling 'really well' when she got home, which was not the case with previous treatments. She compared previous treatments and expressed how with them, 'the journey would start when I got home.' With Kymriah, she recovered 'pretty well and quickly and never picked up any infections.' One young person, who spoke to us three and a half years after Kymriah infusion, expressed they 'thankfully do not live with any late effects from CAR-T.' Although they suffer from late effects of

	treatments prior to CAR-T, they explained 'it is the first time in 8 long years I have felt relatively normal again.' When Kymriah is successful, carers are also able to resume their lives which would have been on pause to undertake carer duties. This was highlighted by a patient who pointed out her parents have 'gone on 4 holidays this year alone to make up for lost time.'
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	When specifically asked about the disadvantages of Kymriah, one young person explained she has 'nothing but positive things to say about it – it saved my life.' However, as with all treatments, patients and their families can be anxious about the potential, serious side effects. One person said a 24-hour headache was the worst of all that they experienced whilst another expressed fatigue and anxiety, amplified by the prolonged period away from home, was the worst. They described the month-long stay in a hotel close to the centre following CAR-T was isolating and compared it to feeling 'like a fish out of water.' The biggest disadvantage for this individual was that although the experience of having and recovering from CAR-T was far better than previous treatments, it did not provide her with a cure. The risks (however small) of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and risk of admission to ICU are considered as disadvantages. However, they are manageable and a reversible risk in the majority. Additionally, it can lead to increased risk of infection in first year but much less than that seen post allogeneic haematopoietic stem cell transplantation. The drawback regarding accessibility and requirement to stay close to the hospital, even after treatment, was also highlighted by other patients we spoke to. Whilst it may not be a significant issue for some, this burden can be very heavy for others who face additional logistical and practical challenges, particularly if they do not have the support of carers. However, our conversations with wider CAR-T recipients highlighted that the requirement to stay within close proximity to the hospital also provided reassurance. The most shared sentiment amongst patients with lived experience of Kymriah and other similar CAR-T products was that the disadvantages and inconveniences of CAR-T are far outweighed by the benefits it provides. From a broader perspective, this will vary as people make their own risk-benefit calculations according to the different barriers and enablers they experience.

13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	If approved for routine commissioning on the NHS, Kymriah has the potential to provide immense hope for many young patients and their loved ones. Its availability, through the Cancer Drugs Fund, has been a game-changer for many who would otherwise have faced palliative care. It meets the needs most important to patients when it comes to new treatments - Kymriah can be curative, no unexpected side effects have been reported in the long-term and is a single treatment that can improve quality of life. It can mean patients have to make fewer hospital visits which will free up staff-time and NHS resource. The overall treatment experiences with Kymriah were described as positive with a faster recovery compared to previous treatments. This means that as it becomes more widely accessible, more patients can reap its benefits. If Kymriah transitions into earlier lines of therapy on the NHS in the future, it could potentially spare many children and young people from futile treatments and their associated toxicities whilst giving them their best chance at a cure earlier on in their journeys.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	

15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment.

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Kymriah is not suitable for the minority of patients that do not express CD19 on their leukaemia. However, patients that do not have a well-matched donor for allogeneic stem cell transplants or those patients who have already had a transplant can benefit more from it. Furthermore, scientific advances can improve our ability to better predict and manage neurotoxicity and other life-threatening effects associated with CAR-T cell therapy. The importance of identifying the right subset of patients who are likely to respond positively to CAR-T cannot be overstated. Biomarker analyses and other methods can aid our identification of the patient subgroups for whom Kymriah can be a definitive option. Therefore, this means those stratified patients can accept CAR-T more confidently which will result in a more effective use of Kymriah. As CAR-T is restricted to only commissioned CAR-T centres, it could cause 'short-lived' geographical inequalities as mentioned below. Kymriah's benefits, influenced by its accessibility, may be unfairly stratified by geographical and socioeconomic groupings.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	We did not speak to anyone who met the eligibility criteria for Kymriah and decided not to commence treatment. However, we have heard of individuals from disadvantaged backgrounds facing additional barriers, such as financial burdens, in accessing CAR-T therapies and that it can act as a deterrent for receipt and uptake of CAR-T.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Geographic disparities have been witnessed in wider CAR-T therapies. Accessing CAR-T in their current set-up can be challenging for some patients who live further from centres and cannot afford, for financial or logistical reasons, to travel longer distances. However, this issue should become less significant as it become more widely accessible through increased delivery centres and financial assistance. However, there is a possibility that this potential inequity in access, although expected to be short-lived, could be prolonged if the right measurements to increase accessibility are not in place. Stakeholders should keep access considerations in mind and actively aim to reduce barriers.

More broadly, there are unjustifiable age discriminatory rules about who can access certain treatments. Age cut-offs that disallow a potentially effective treatment to those who have exhausted all treatment options, due to a birth year on the wrong side of the approval criteria, can be very hard for patients and their loved ones to comprehend. A more pragmatic and empathetic approach would be welcomed.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Acute lymphoblastic leukaemia is a devastating diagnosis for children, young people and their loved ones and can be a very isolating and challenging time as they deal with symptoms of the diseases coupled with the treatment toxicities.
- Treatment is long, unpleasant and burdensome which often brings with it a high risk of acute and long-term side effects. This has huge impacts on patients' long-term health, anxiety about risk of relapse, interruption of study and work and isolation from peers.

- There is a significant unmet need at this line of treatment as patients with relapsing/refractory disease face very limited options. Kymriah, with its curative potential, offers those with limited options a chance at achieving a cure and meets the needs identified as most important to patients.
- Although treatment with Kymriah can be intense and side effects can require intensive care, it is short in duration and recovery is often quicker which has significant positive effects on patients' overall treatment experience. Many patients and their loved ones describe the disadvantages of Kymriah are far outweighed by the benefits it can provide.
- Kymriah's potential side effects and restricted availability are a cause for concern and imposes burdens for some group of patients. Whilst acknowledging that and the high cost, to reject a therapy that has been described by patients as their 'last real option' can be very difficult to comprehend and will continue to leave the significant unmet need in this treatment setting unresolved.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected by leukaemia, MDS or MPNs receives the best possible diagnosis, information, advice, treatment and support. Approximately 80% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 20% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the	**Amgen:** £5,000 support services **Incyte:** £30,000 core funding **Novartis:** £25,000 core funding, £25,000 for videos, podcasts and webinars and £487 honorarium **Pfizer:** £10,000 core funding **Servier Labs:** £5,000 core funding **Takeda:** £30,000 core funding and £855 honorarium

appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission has been informed by a patient experience survey of 151 adults diagnosed with acute lymphoblastic leukaemia (ALL), carried out by Leukaemia Care in 2016. This was part of a wider survey of 2,019 leukaemia patients entitled 'Living with Leukaemia'. The results of this survey were published in September 2017 and are available online at: www.leukaemiacare.org.uk/living-with-leukaemia. ALL specific breakdowns of the data (16-24) have been used to inform this submission. We have no reason to believe that the patient experience evidence provided from 2016 has changed since between then and now, unless specifically stated in the submission. In 2021 we conducted a survey for ALL patients to understand their views on treatment options. Some of these findings, including statistics and quotes, have been included in the submission. We also spoke to some patients on a one-to-one basis, to understand more about their experience, these conversations have been reflected as quotes in the submission.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. As of 2018 there are 791 new cases of acute lymphoblastic leukaemia in the UK each year. The highest incidence rates of ALL are in children aged 0-4, after which the risk of ALL drops gradually, but starts to increase again at age 50. Five-year survival outcomes vary greatly by age, from over 90% in the under 15s and falling gradually to approximately 58% in those aged 15-39. However, in the relapsed/refractory setting, survival is significantly reduced with approximately 10% of all patients surviving 5 years. In a meta-analysis of research by Clarke et al. (2016), the most common clinical presentations of childhood leukaemia were identified as: hepatomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%), bruising (52%), recurrent infections (49%), fatigue (46%), and limb pain (43%). The common symptoms reported by 16-24-year olds following diagnosis include fatigue (90%), nausea or vomiting (60%), feeling weak or breathless (60%), sleeping problems (45%), headaches (40%), lower backpain (40%), and weight loss (40%). One ALL patient we spoke to who was 20 years old when she was diagnosed also reported severe headaches and neck pain, claiming that "*nothing would make the headaches go away*". Due to the rapidly progressing nature of the condition, 63% of adult patients had only experienced symptoms for less than a month before visiting their GP. ALL is similarly as rapidly progressing in children and young people. The NCIN/NCRAS 'Routes to Diagnosis' report shows that 64% of all ALL patients are diagnosed via emergency presentation (of which 42% were A&E, 27% emergency GP referral, 5% inpatient emergency and 26% outpatient emergency). This compares to a cancer average of 22% and is the highest of any cancer type in the report. The rapidly progressing nature of the condition means that 86% of ALL patients start treatment within a week of diagnosis.

	Being diagnosed with ALL can also have a significant emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation, and depression. This can be particularly difficult for children and young adults. In our 2016 survey, two thirds of 16-24 years old reported feeling more depressed or anxious since diagnosis. There are also practical impacts of an ALL diagnosis; with our 2016 survey showing that 58% of 16–24-year-olds experiencing pain as a direct result of their condition (37% occasionally, 16% regularly and 5% constantly). Additionally, 45% have difficulty moving around (sometimes 30%, often 10% and always 5%) and 60% have difficulty performing some of their daily routines, such as cooking or cleaning. Another 37% reported that they have problems taking care of themselves. The financial impact on a young person can also be significant. In our 2016 survey, 80% of 16-24-year-olds had to reduce their hours in education or employment with the majority having to stop completely (45%). This impact has likely worsened recently with the rising cost of living in the UK. Leukaemia Care's conducted research in 2023 for our #LeukaemiaLevy campaign, to understand more about the financial impact on patients in the current climate. Leukaemia Care found that the number of patients reporting to have been affected financially since diagnosis has increased from 43% in 2017 to nearly 60% in 2023. On average, patients with acute leukaemia were more likely to experience both an increase in living costs and a decrease in their income compared with all leukaemia patients combined (75% vs. 54.5% respectively).
7. What do carers experience when caring for someone with the condition?	The emotional impact does not affect the patient in isolation. A diagnosis of ALL in a child or young person can place huge emotional strain on families and friends, many of whom may be affected. As such, improvements in a patients' treatment and quality of life will also have a wider impact on the lives of their family and friends. An ALL patient we spoke to who was 20 at diagnosis said: *"The impact that my diagnosis had on my family was profound. Initially, shock was the overruling emotion felt by them in the first few weeks. We had to try and explain everything to my niece, who*

	was just 6 at the time. It was so difficult for all of them to even begin to process what was happening." In addition to the emotional impact, ALL can also have a practical and financial impact on the patient's family. For young people this financial impact can be direct, but the financial impact can also impact the patients' family e.g., parents, especially for younger children, as both caring responsibilities and costs increase. This can have a knock-on effect on anyone in the family, including siblings. The patient went on to say: *"My mum had to stop working as a shop assistant so that she could support me when I was in the hospital and whilst I was at home in between treatments. She became my main carer. My dad is self-employed and had to continue working throughout my treatment to support us and to keep paying the bills. Even after working all day, he would still make the trip to the hospital every single day, rain or shine. It was really tough on all of us, but we got through it together."*
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	When we asked in our 2021 survey whether ALL patients thought existing treatments for this disease were sufficient, 100% of respondents said no or not sure. One major reason for patients with ALL to claim that current treatments available on the NHS are insufficient is that other than CAR-T, there are no other treatments providing a potential cure in the relapsed/refractory setting (i.e., post stem-cell transplant). Other therapies and comparators available in the relapsed/refractory setting include salvage chemotherapy, which is used if a patient has not responded to prior chemotherapy treatments. However, salvage chemotherapy only extends patient lives by a matter of months. CAR-T is now more available to patients than before, for example as a result of having CAR-T products in the CDF, but these are only temporarily available. A permanent option is of paramount importance to young patients in the relapsed/refractory setting who otherwise have very few options and whose outcomes are poor.
9. Considering all treatments available to patients are	Because CAR-T products are only temporarily available to patients via the CDF at present, there is still a significant unmet need for a potentially curative treatment in the relapsed/refractory setting as part of routine commissioning on the NHS. This is because current treatment options in

there any unmet needs for patients with this condition? If yes please state what these are	the setting are very limited and there are no other potentially curative treatments. As such patients with relapsed/refractory ALL often have poor outcomes. There is therefore a strong unmet for a treatment which can achieve and maintain remission for young patients, who have exhausted all other treatment options. Losing access to CAR-T would therefore result in this unmet need being further exacerbated. When we asked ALL patients about the most important features of a new treatment, in the 2016 survey, improved quality of life and improved/longer survival came out on top for 16-24-year-olds, as selected by 85% of respondents. This shows an unmet need for a treatment which satisfies these criteria, and in the patients, we've spoken to who have had CAR-T they have seen an improvement in both quality of life and longer survival, including to the point of complete remission.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	We were not able to find a patient to speak to who knew that they were treated with CAR-T under the MAA. We have, however, spoken to patients who were treated with Kymriah (the same as the product being reviewed) since it's approval via the CDF. The patient we spoke to who was 20 when she relapsed and 21 when she received CAR-T in 2019 told us: "*When we found out that I had relapsed after my stem cell transplant, we were all terrified, until we found out about CAR T therapy. At the time I was told I needed the treatment, it wasn't available at my hospital, so we were told that we may have to self-fund accommodation during the treatment. This was quite scary to think about, as we were still living on one income. However, we*

	would have made it work nonetheless. Fortunately, I was able to have my treatment at my local hospital, so we did not have to stay away from home for my treatment." With more and more CAR-T centres being set up since 2019, this will have reduced accessibility issues and travel requirements for patients to some extent. Furthermore, charities often offer financial support for treatments, such as Leukaemia Care's away from home fund (specifically for CAR-T patients), further removing accessibility issues for some patients. Longer and more certain access arrangements could help speed up access to the treatment to more patients, as there is more incentive to invest in the skills and technology needed to deliver treatment.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	*When we got the news that I was in remission, everyone was elated. We had a delayed 21st birthday for me to celebrate a couple of months later - it was truly wonderful. Shortly after my treatment had finished and my remission was confirmed, I was well enough to return to university, which subsequently meant that my mom was able to return to work within around 3 months of my treatment ending. My remission made my family feel like they were finally able to breathe again, after months of holding our breath, wondering if this last-ditch effort to save my life would work. 4 years later, we are all still sighing with relief that we were lucky enough to be able to have this treatment as an option. Without CAR T, I wouldn't be here today."* This is a treatment which truly can save young people's lives, as it did in the case of the patient we spoke to for the purpose of this submission.
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Some of the side effects of CAR-T can be a disadvantage of the therapy. Clinicians informed us of the severe short-term side effects, e.g., cytokine release syndrome (CRS) and neurological changes which manifest in an inability to write clearly, for example. CRS occurred in 24% of patients and neurologic events occurred in 25% of patients, but clinicians and clinical trials have reported that these side effects are temporary and reversible.

	The patient we spoke to who was 21 when she received CAR-T explained that even though she had few side effects, she was taken to ICU due to low blood pressure. She commented *"we had some scary moments, such as a trip to intensive care, but we also had some really nice moments too."* The patient's trip to ICU was for monitoring purposes only and her low blood pressure was reversed quickly with the drug Tocilizumab. This demonstrates that many of the side effects can be easily managed or reversed, and as previously mentioned, the recipient of CAR T said that her experience of it and the side effects were "*a stark contrast to what I had already been through with my stem cell transplant"*. This is partly because of the duration of time which she experienced the side effects of SCT, telling us that she was sick regularly for 3 months post-transplant. For the patients we spoke to the side effects of CAR T were felt for a much shorter period, partly due to their nature of being quickly managed and reversible. Furthermore, in the 2016 survey 80% of the 16-24-year-olds said 'yes' when asked if they would be willing to experience additional side effects for a more effective treatment. Another disadvantage is that CAR T therapy does not guarantee a cure in every patient. In fact, it only works as a cure in 50% of patients who are treated. But, given that this is already in the relapsed/refractory setting and the outcomes for patient's survival at this stage are poor, 50% of people achieving a cure is a significant improvement compared with the alternative of best supportive care and death.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	As previously mentioned before, there is a significant unmet need in this cohort, which removing access to CAR-T would expose. The treatment has saved the lives of patients we have spoken to and without it their chances of survival would have been extremely low or none. There are no other potentially curative options in this setting/part of the pathway.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	As mentioned, we were not able to find a patient to speak to who knew that they were treated with CAR-T under the MAA. The patient we spoke to who had Kymriah believes it could have been an individual funding request via national panel at NHS. As such we are unable to fill out Section 4. N/A
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	N/A
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	N/A

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	N/A

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Not that we are aware of. We believe it to be rare that anyone who is eligible would not start treatment as this is often a last resort treatment, when other treatments have failed or not been suitable. Sometimes, finances could be a barrier, for example if the nearest CAR-T centre is far away and would result in high travel costs/hotel stays for family/carers. However, this rarely leads to a patient not receiving treatment as there is some support in place from the NHS and the charity sector for situations like these.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NHSE submission – CAR T tariff costs

Applying the new 2023/2024 contract values to the eligible population for ID6290, weighted in line with historic activity levels (see below), would suggest the application of a blended tariff value of £98k:

Table 1. Updated CAR-T tariff costs

	Patients treated 2018 - Sept 23			
Age bracket	**Grand Total**	**%**	**Tariff**	**Weighted Tariff**
18 or under	110	83%	£106,504	£88,086
19 or older	23	17%	£56,740	£9,646
Total	**133**			**£98,044**

As this tariff work was still being finalised at the point of calculating the initial anticipated budget impact of this appraisal, this was compiled using the information from the previous adult appraisals and the existing paediatric tariff as follows:

Table 2. Tariff costs included in budged impact assessment for ID6290 (tariff applicable to this appraisal)

	Patients treated 2018 - Sept 23			
Age bracket	**Grand Total**	**%**	**Tariff**	**Weighted Tariff**
18 or under	110	83%	£106,504	£88,086
19 or older	23	17%	£41,100	£7,108
Total	**133**			**£95,194**

Given the relatively immaterial difference in the overall value, due to the weighting towards younger patients, and to take a consistent approach with previous CDF exit appraisals in the current financial year, it is considered reasonable to stay with the original blended value of £95.2k.

From 2024/25 onwards, it is proposed that the value of £56,740 would be the appropriate value for the initial assessment of any new CAR-T indications or reassessment of any CAR-T CDF indications for patients in the age bracket 19 or older.

Table 3. Case mix by age group

Table 1	Financial year						
Age bracket	**18/19**	**19/20**	**20/21**	**21/22**	**22/23**	**23/24 (YTD*)**	**Grand Total**
18 or under	4	13	30	20	27	16	110
19 or older		2	5	3	10	3	23
Total	**4**	**15**	**35**	**23**	**42**	**19**	**133**

For ID6290, the paediatric tariff is £106.5k, the adult tariff is £41.1k and the blended tariff is £95.2k.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access

Clinical expert statement

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Sara Ghorashian**

NICE National Institute for Health and Care Excellence

2. Name of organisation	**Great Ormond Street Hospital for Children**
3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): I have translated novel CD19CAR T cell products from bench to clinical studies
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain I have received speakers honoraria and conference support from Novartis in the past 5 years I hold patents and have potential for royalties in the CD19 CAR T cell therapy field through University College London Business
7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
The aim of treatment for this condition	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: Tisagenlecleucel is given with curative intent although long term follow-up data are not available (3 year EFS recently reported, DOI: 10.1200/JCO.22.00642)

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A complete haematological response (<5% blast count in the bone marrow and absence of disease detectable in the CSF and at any other extramedullary sites) with or without haematological recovery and with an absence of measurable residual disease by flow cytometry or molecular testing
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival Y This answer is supported by a recent publication providing an efficacy comparison of tisagenlecleucel with real-world historical standard of care therapy using patient-level data and propensity adjusted indirect comparisons. This study was undertaken in a European context and thus relevant to delivery in the UK. The study (https://doi.org/10.1038/s41375-023-02042-4) showed favourable outcomes for tisagenlecleucel compared to standard of care therapy in terms of overall, event free and relapse free survival (survival probability at 2 years was 59.49% for tisagenlecleucel vs. 36.16% for SOC population, 42.31% vs. 30.23% and 59.60% vs. 54.57%, respectively) Increased time to progression Y Improved QOL Y Patients and their families report again and again (including in a consultation I have had this week) that the patient feels better following tisagenlecleucel infusion than they have done since diagnosis with acute lymphoblastic leukaemia.

	We have been able to rehabilitate patients to a better level of generalised ability than since diagnosis which is when cumulative toxicities from standard chemo/radiotherapy start to take effect Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y: Improved quality of life for carers in view of reduced hospital visits and better state of health of the patient they are caring for Non-health benefits. Ability to return to school/ education/ work for both the patient and carers Improved self-esteem both for the patient and parents / family Ability to care for others in the family for both for the patient and carers Improved social and physical development for the patient Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y please explain: Parents of patients can be more productive as they are able to return to work due to the fact that tisagenlecleucel is a living drug requiring only a single infusion and associated monitoring Implications for delivery of the NHS service N, please explain: This is a reappraisal of a drug already in NHS delivery. There is not expected to be a significant change in the numbers of patients treated with tisagenlecleucel for this indication and as a result, there should be no implication for ongoing delivery within the NHS
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life Delivery of the therapy requires an inpatient stay (although ambulatory models are being tested) for generally 3-4 weeks. There are short term acute side effects which generally arise in the context of hospital delivery and can persist for up to 4-6 weeks but they generally have a duration of days and the vast majority lead to complete recovery with no long lasting effects (unlike the long term toxicities of stem cell transplantation and standard chemotherapy)

12.Are there any important outcome data that were not collected during the managed access period?	Quality of life was not formally assessed in the managed access period but our patients again and again tell us that they feel better than they have done since pre-diagnosis and their ability to be rehabilitated to levels of health / ability that are better than was possible during standard therapy is testament to this.
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	A persisting CAR T cell product that can be used as a standalone therapy with a minimal relapse rate. Tisagenlecleucel therapy is the only effective therapy available for this patient cohort
14. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that	There are no alternative effective therapies for patients in second or greater relapse or for those who relapse post stem cell transplantation: Patients in the UK receive blinatumomab for first relapse and re-treatment is not reimbursed on the NHS should they have a second relapse, nor have outcomes been defined for re-treatment Patients who have had a first transplantation procedure generally do not get offered a second stem cell transplant because of significant procedural mortality of 25-30% and poor efficacy because of high relapse rate leading to an overall survival of 25-40% (doi: 10.1016/j.bbmt.2018.09.016) Patients who meet eligibility to proceed to stem cell transplant because of poor risk disease and low predicted EFS who have co-morbidity or lack of a suitable donor have no effective alternative therapies All these groups are benefitted substantially by having access to Kymriah as a potentially curative option Data supporting improved outcomes compared to standard of care therapy in this context has been discussed in point 10 above.

current need is met?	
15. Are there any groups of patients who might benefit more or less from the technology than others?	Please see point 14 Patients with a low disease burden <5% pre lymphodepletion have a better EFS than those with a high disease burden. This appears to be the most reliable indicator of outcomes post CAR T cell therapy in the largest real world datasets
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Combination chemotherapy is given in front line therapy https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/UKALL_2019_Interim_Guidance_Final.pdf Blinatumomab + combination chemotherapy or stem cell transplantation is given in first relapse. CLCN UKALL2019 guidelines, UK Relapse guidelines. https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/2021_Relapsed_ALL_UK_Guideline_V1.3_16_02_2022.pdf There are no effective or established therapies in second or greater relapse or relapse post stem cell transplant other than CAR T cell therapy BSBMTCT CAR T cell therapy practice guidelines for paediatric ALL are in development and the first (of 3 phases of care) has been accepted in British Journal of Haematology

17. Are there other clinical pathways used in England other than those recommended in the guideline?	Y/N, please explain important differences and why they occur: Generally no other pathways are used, except in some areas, where adults aged 21-25 are treated on adult pathways rather than the paediatric ones described here. In general, since there is evidence that younger adults have better outcomes if treated on paediatric regimens, the therapy of young adults should follow paediatric practice in any case
18. Would the new technology require a change in the clinical pathway?	No – this is a reappraisal and clinical pathways are already established and successfully delivering the service with outcomes as good as seen in clinical studies (UK real world
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	Cost to NHS has been defined by a recent NHSE costings exercise Patients are only eligible for paediatric CAR T therapy in 4 UK centres and therefore often have to travel to receive the care. They are eligible for charitable grants (e.g. from Leukaemia Care, YLVC), but these do not fully cover costs or loss of earning for parents or patients
20. If there are any rules (informal or formal) for starting and stopping	NHSE service specification for CAR T cell therapy of paediatric ALL defines eligibility and delivery criteria Eligiblity is then confirmed by discussion in the National UK CAR T cell therapy panel for paediatric ALL (this is undertaken on a voluntary and not mandatory basis, unlike patients treated for lymphoma)

treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	Since this is a living drug, only a single infusion is indicated / licensed, so no stoppage rules apply
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: CAR T cell therapy delivered on the NHS for these indications often represents the only effective therapy for patients with advanced B-ALL. Patients are therefore very grateful to be given a therapeutic option delivered with curative intent where none previously existed We have collected real world data on outcomes of NHS patients treated with tisagenlecleucel in the UK and demonstrated similar outcomes to those on the ELIANA study, and if anything, rates of severe acute toxicity were lower. These data have been submitted for publication and have been submitted to the EAG for consideration Negative: Lack of persistence of tisagenlecleucel CAR T cells occurring within 6 months of infusion is a major cause of treatment failure since this is associated with a high risk of relapse with CD19 positive disease. This risk has been defined on the basis of data from combined clinical studies

	(DOI: 10.1158/2643-3230.BCD-21-0095) and from real world datasets (DOI: 10.1038/s41375-021-01281-7). The frequency of therapy failure due to lack of persistence is higher in real world delivery than was seen in the pivotal ELIANA study (DOI: 10.1056/NEJMoa1709866)
22. Did any people decline treatment? What were their reasons why?	Where there were better predicted outcomes between stem cell transplantation and CAR T cell therapy, some patients favoured to proceed to stem cell transplantation directly and were prepared to accept the greater therapy related toxicity of this approach
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	The management and monitoring of patients has been generally straightforward with protocolised management of acute severe toxicities according to international consensus guidelines (DOI:https://doi.org/10.1016/j.bbmt.2018.12.758), and an NHS pathway for delivery of immunoglobulin replacement therapy for those with hypogammaglobulinaemia (https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf) We have developed and validated assays for CAR T cell persistence to aid physicians in decision-making following CAR infusion.
24. Would routine assessments in clinical practice differ from those that comprise the	Not substantially

MAA monitoring? How?	
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	As a community of paediatric CAR T cell therapists, we have formulated national treatment pathways and care. We are in the process of writing therapy guidelines to assist health care professionals (first guideline accepted for publication in British Journal of Haematology) and we have defined outcomes of patients treated on the managed access scheme (submitted to Blood Cancer Journal). We have demonstrated that patients treated in centres with expertise in delivery of this therapeutic specifically for paediatric ALL can achieve equivalent outcomes to those seen in the pivotal study
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: UK real world data on outcomes following tisagenlecleucel delivery for paediatric B-ALL (submitted for consideration to Blood Cancer Journal) have been considered by the EAG Yes for the comparator, please give link:

Equality	
27a. Are there any potential equality issues that should be taken into account when considering this treatment?	As an expert in the delivery of CAR T cell therapy for paediatric ALL, I believe that the best outcomes are obtained when centres manage a higher number of cases (at least 5-10/yr) than having many centres dealing with a very few cases. This may mean that patients have to travel to receive the therapy but when we have asked our patients for their opinion, they have always preferred to travel further to receive care if it is of a higher quality. Further, equality of access is assured through: 1) A geographic spread of centres delivering CAR T cell therapy for paediatric indications 2) Discussion of all patients with relapsed leukaemia in a national panel which convene on an alternate weekly basis, in which appropriate patients are identified as potentially be eligible for CAR T cell therapy 3) Discussion of all cases that may be eligible for paediatric CAR T cell, identified as per 2) above, in a national panel which convenes on an alternate weekly basis

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access

Clinical expert statement

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Prof Persis AMROLIA**

NICE National Institute for Health and Care Excellence

2. Name of organisation	**Great Ormond St Children's Hospital, London**
3. Job title or position	**Director BMT/CART unit**
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain **I have no COI in relation to this product**
7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: curative Other, please describe
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Achievement of molecular remission in the marrow with no evidence of extramedullary disease

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

x cm, or a reduction in disease activity by a certain amount.)	
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival Y Increased time to progression Y Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? Reduced treatment related mortality and late effects compared to Stem Cell Transplant Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y, please explain: compared to Stem Cell Transplant, Tisagenlecleucel requires shorter inpatient stay with a faster return to normal life for the patient and family Improved accessibility to patients Y/N, please explain: Implications for delivery of the NHS service Y, please explain: Shortened duration of admission compared to SCT

11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life 1. Cytokine Release Syndrome (incidence 60%, severe <20%): can make patient critically ill with hypotension/hypoxia requiring PICU support but manageable to Tocilizumab/steroids and self limiting with no late effects 2. Neurotoxicity (incidence 20-30%, severe < 10%): can affect speech, cause fits, impair conscious level. In general resolves either spontaneously or with steroids without long term sequelae. Severe neurotoxicity is rare with Tisagenlecleucel in children. 3. Prolonged cytopaenias (incidence 20- 40%); Can predispose to infection but generally responds to G-CSF support and self-resolves over time 4. Hypogammaglobulinaemia is almost universal in CAR T cells persist and the risk of infection is mitigated by immunoglobulin replacement
12.Are there any important outcome data that were not collected during the managed access period?	Loss of CAR T cell persistence (as evidenced by loss of B cell aplasia) is the major cause of treatment failure in the real world. I do not know if NHSE collected data on loss of B cell aplasia and the need for further therapy eg consolidative SCT. In a real world analysis of 125 UK patients treated with Tisagenlecleucel for r/rALL in addition to the 40 patients who had morphological/molecular relapse, 22 patients needed further therapy for early loss of B cell aplasia (Oporto-Espuelas et al submitted).

13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Whilst Tisagenlecleucel is generally well tolerated and offers a 40% chance of cure to eligible patients, many patients relapse either because of evolution of CD19 negative disease or due to loss of CAR T cell persistence. There is a clear unmet need to develop novel CAR T cell therapies that overcome these 2 challenges. Moreover, there are patient groups such as those with isolated CNS relapse post-SCT who are not formally eligible for Tisagenlecleucel by the NHSE criteria where there is increasing evidence of clinical benefit without increased toxicity (Leahy Lancet Haematology 2021). In addition there are other groups eg high risk first relapse and high risk infant ALL who were not included in the ELIANA study and who are therefore not eligible in whom the use of Tisagenlecleucel should be evaluated in order to determine if it can be used instead of Stem Cell Transplant which is clearly more toxic both in the short and long term.
14. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This ground-breaking new technology has enabled long term cure in 40% of patients who relapse after Stem Cell Transplant and were previously incurable. Likewise for patient with refractory disease and those in 2nd or greater relapse, it offers the potential to avoid the need for Stem Cell transplant with its attendant 10-20% mortality, acute complications including GVHD and late effects.
15. Are there any groups of patients who might benefit more or less from the technology than others?	Patients with high disease burden, those with non-CNS extramedullary disease and those who have not responded to prior therapy with Blinatumomab are less likely to respond to Tisagenlecleucel.

What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Y Frontline therapy as per ALLTOGETHER1 study Relapse therapy as per UK relapsed ALL guidelines 2021 Tisageneleucel is used as per NHSE/NICE guidance at approved centres following determination of eligibility at the fortnightly National ALL CAR MDT
17. Are there other clinical pathways used in England other than those recommended in the guideline?	N
18. Would the new technology require a change in the clinical pathway?	N- pathways already incorporate Tisagenleucel in treatment algorithms for eligible patients
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	Y- costs for admission, treatment in intensive care for severe CRS/neurotoxicity, treatment of CRS with Tocilizumab, treatment of hypogammaglobulinaemia with immunoglobulin replacement.

20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	Not applicable as this is a one off therapy and the indications are likely to remain the same when starting treatment.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: Good safety profile which is much less toxic than Stem Cell Transplant and achieves complete remission in 90% of patients. Negative: Significant risk of treatment failure due to loss of CAR T cell persistence and to a lesser extent CD19-ve relapse.

22. Did any people decline treatment? What were their reasons why?	Very occasional patients who were also eligible for transplant preferred this as the established standard of care
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	This necessitates a dedicated CART clinical nurse specialist and it would be helpful to have more support for data management. With the appropriate support these assessments were straightforward and proportionate
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	At our institution we would continue to monitor in the same fashion.
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	No

Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: Analysis of real world data: Pasquini et al Blood Advances 4 (21)5414-24 (2020) UK data: Oporto-Espuelas et al submitted.Please contact Dr Ghorashian (senior author) for manuscript. Yes for the comparator, please give link:
Equality	
27a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory B-cell acute lymphoblastic leukaemia or caring for a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. **Please note that you do not have to answer every question** – they are prompts to guide you.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 2 February 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia

Table 1 About you, relapsed or refractory B-cell acute lymphoblastic leukaemia, current treatments and equality

1. Your name	Sophie Wheldon
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory B-cell acute lymphoblastic leukaemia ? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Leukaemia Care
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory B-cell acute lymphoblastic leukaemia ? **If you are a carer (for someone with relapsed or refractory B-cell acute lymphoblastic leukaemia) please share your experience of caring for them** Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	I was diagnosed with B-cell acute lymphoblastic leukaemia (B-ALL) in June 2018 when I was 20 years old. I had been experiencing a range of non-specific symptoms for around 2 months prior to my diagnosis, including persistent headaches, neck pain, and a lingering chest infection. I initially disregarded my symptoms as I was studying at University at the time, so I believed I was just a bit run down. After a trip to see the GP and an urgent referral to A&E, I received my diagnosis within 48 hours. It was a complete shock to both myself and my family. After undergoing numerous chemotherapy regimens (UKALL2011, NOPHO-B, and NOPHO-C) I underwent an allogeneic stem-cell transplant in November 2018. The transplant had a significant impact on my mental and physical health, and I suffered from severe side effects including extreme weight loss, prolonged fatigue, and struggled with infections, sickness and vomiting for many months after. It was an incredibly difficult time in my life, and is something that still impacts me now. My mom took a significant amount of time off from work to become my full-time care giver when I was diagnosed. She stayed with me every night that I was in hospital. My dad is self-employed, so he had to carry on working to pay the bills whilst my mom stayed with me. It was really difficult for them both to deal with, both financially and emotionally too. My niece, who was just 7 at the time of my diagnosis, found it

	really hard to understand what was happening. It was incredibly an incredibly challenging time for us all as a family to cope with my diagnosis. When I relapsed in April 2019, I was advised that there were very few viable treatment options available for me, with things like chemotherapy or a donor lymphocyte infusion looking likely to be futile. This news was extremely difficult to cope with mentally for both myself and my family, and we all felt very isolated. Essentially, the news was that I was terminally ill from that point forward, which was a lot to comprehend at just 20 years old. This was until we found out that CAR T-therapy could be an option, which gave us so much hope in such a dark time. Despite this hope, we were told at the same time that I would likely need to travel to a specialist centre for the treatment and stay nearby for at least 4 weeks following the infusion, as it was not yet available at my treatment centre (Queen Elizabeth, Birmingham). We were advised that this would need to be self-funded, which would have caused a massive financial strain on my family, as my parents would have had to support me with this. The thought of this was terrifying to me. At the time of my relapse, my mom had recently returned to work, so she then had to take more time off from work to take care of me. It was very worrying. Thankfully, I was lucky enough to be able to have my treatment at the Queen Elizabeth and was the first patient in the Midlands to receive tisagenlecleucel for relapsed B-ALL.
7a. What do you think of the current treatments and care available for relapsed or refractory B-cell acute lymphoblastic leukaemia on the NHS?	**7a.** Other than CAR T therapy, there are no other treatments that offer a potential cure to patients who have relapsed/refractory B-ALL. When I was told that I relapsed, I was advised that other treatments such as salvage chemotherapy or a donor lymphocyte infusion wouldn't have much of an impact on my leukaemia and would likely make me feel quite unwell, which was the opposite of what we wanted to achieve. These treatments may have extended my life by a matter of months,

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	which in retrospect, is nothing in comparison to the 4.5 years (and counting!) that I have had since receiving tisagenlecleucel in June 2019. **7b**. Other patients who I have connected with previously have expressed their anxiety about there being no permanent option available to sustain a chance of cure in this group. There are no comparable options available for our cohort that offer the chance of surviving for more than just months, which is scary to comprehend and clearly demonstrates that there is an unmet need for patients within this group to have access to such a treatment.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory B-cell acute lymphoblastic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As mentioned above, there are very few options available to patients who have relapsed or refractory B-ALL. I was advised that chemotherapy would have little to no impact on my leukaemia at that stage, and that a donor lymphocyte infusion would be likely to cause significant graft vs. host disease (GvHD) in myself which would overall be quite unpleasant. These options were never offered as a cure, but only to potentially extend my life by a little, and even that was never guaranteed When I was told that I might be able to have a DLI, I felt sick with fear and anxiety because I was scared that it would be like my transplant. I did not want to develop GvHD and I did not want to feel as awful as I had felt before because I knew how bad it could get and how long it would take to recover. If I would have needed a second transplant, I know that my mental and physical health would have suffered greatly. I don't think that I would have been able to cope with that again in retrospect.
9a. If there are advantages of tisagenlecleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	**9a.** Unlike other treatment options for this cohort, tisagenlecleucel offers a chance of achieving a cure from a disease which would otherwise be terminal in these patients. I was quite anxious going into treatment because I was very worried about the unknown, and that it would be like my transplant experience. I had not had any opportunities to speak to other patients in my age group who had been through the treatment either, so I had lots of unanswered questions. Despite the anxieties, I was

	so relieved to find out that my experience was nothing like what I had been through previously. One of the benefits was the reduced amount of time spent in hospital. I received all of my conditioning chemotherapy as an outpatient due to living relatively close to the treatment centre, which was a bonus. The conditioning protocol was far less intensive than the one I had experienced previously with my transplant, and I was hugely relieved to have not needed any further radiotherapy. The time spent as an inpatient was also substantially shorter with CAR T at 11 days vs around 4-5 weeks for transplant. This was a big boost to my mental health after having spent so much time in hospital over the previous 12 months. The impact on my quality of life was immense. After feeling so unwell for so long, I felt like I could say that I was feeling “better” for the first time, shortly after my infusion. Again, this had a very positive impact on my mental health and helped me to progress and continue getting better. The physical recovery was much smoother than what I had previously experienced with the transplant. I was seen 3 times per week in clinic for blood tests and for supportive transfusions, but I really appreciated this as I knew I was being monitored closely – it gave me a lot of peace of mind to know that the team were keeping an eye on me. As I had mentioned previously, I was a student at University before my diagnosis. I had to take some time out from my education, which was really difficult mentally. After my transplant, there was no way that I could have even thought about getting back to university. However, CAR T allowed me to get back to my studies within 3 months. I returned to university in the September to live in halls of residence, and graduated with a First – I couldn’t have returned so quickly if it wasn’t for CAR T.

	Not only was CAR T effective in the months after my infusion, but years after, too. It has been more than 4.5 years since I was told that I was in remission, thanks to tisagenlecleucel. The side effects were much more manageable that those that I had experienced with my previous treatments. I look back every day and remember how I felt on the day I was told that I was in remission. I will be forever thankful to have been able to access the treatment, and cannot imagine what might have happened if I wasn't able to have it.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	**9b**. I would say that the most important advantage of receiving CAR T therapy for me was the unexpected and rapid return to 'normal life'. For someone who had been feeling so unwell for so long, it was a massive relief to finally be able to say that I was starting to feel better. The follow up period was intense at times, but it was made better by having such a supportive healthcare team around me. All I could think about was how much easier this had been in comparison to my transplant and prior treatments. To be able to start getting out and about, and to get back to University within 3 months of having my treatment was just a dream come true. It felt to me like I was able to regain some control in my life during a time where everything felt completely chaotic. CAR T was a welcomed calm to such a vicious 12 months myself and my family. Without CAR T, I would not have been able to get back to my studies when I did. I would not have been able to go out with my family without feeling violently ill, as I had done before with my transplant. CAR T truly gave me my life back.
9c. Does tisagenlecleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	**9c**. Yes. As tisagenlecleucel was derived from my own cells, there was no risk of rejection or GvHD. This was a big relief, as I was extremely anxious about whether the side effects of CAR T would be like the ones I had with transplant. I felt nowhere near as awful as I had felt with my transplant. With CAR T, I felt like I could function

	again. I felt like myself again, after such a long and gruelling year. It was a welcomed surprise.
10. If there are disadvantages of tisagenlecleucel over current treatments on the NHS please describe these. For example, are there any risks with tisagenlecleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	In order to receive CAR T, you must be relatively well in order to undergo the apheresis process, and also to wait for the cells to be manufactured, which can take around 4 weeks. This might be difficult for some cases, as some relapses are more rapid than others and therefore tumour burden might be more difficult to manage during this period in some patients. The side effects of CAR T can vary in severity, which can be an issue for some patients. I was relatively lucky and experienced grade II CRS, which was treated effectively with 3 doses of tocilizumab and 24 hours in intensive care to monitor the low blood pressure that I began experiencing around day 3-4. I am aware that some patients experience severe CRS or neurotoxicity, which can sometimes be fatal. This is a risk that must be considered carefully by patients before consenting to the treatment. I was extremely lucky to have been able to have my treatment at my consulting hospital, but I am aware that others may live much further away, meaning they will need to pay out for any costs associated with travel and accommodation during and after their treatment. This can be very difficult, especially given the ongoing cost of living crisis that is affecting many cancer patients and their families. The long term effects of CAR T therapies are still being explored. I have personally experienced long-term immunosuppression following my infusion, which is now being very well managed through monthly immunoglobulin infusions (IVIG). Whilst this could be viewed as a disadvantage by some, as a patient, I am more than happy to go into hospital for a couple of hours each month, as I know that I am getting some additional protection from infection. The most important thing is that I am alive and well.

11. Are there any groups of patients who might benefit more from tisagenlecleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	A major benefit of tisagenlecleucel is that it is an autologous therapy. This means that there is no need to find a tissue matched donor, which can be notoriously difficult for patients who are from an ethnic minority or those with mixed heritage. Removing this barrier would give many more patients a chance to survive their disease, regardless of their background. Patients who live further away from a treatment centre in more remote areas may benefit less from this treatment, as they will be at a disadvantage when expected to travel and remain close to a treatment centre for a minimum of 4 weeks post infusion. This will be likely to cause both financial and psychological strain on those particular families.
12. If you have experience of this treatment during the period of Managed Access please tell us your views on the results from tests and assessments that have been used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	My consultant advised me that my case would be taken to the National CAR T NHS panel for discussion, and the decision to go ahead with this treatment for me was made following this meeting and based on my latest bone marrow results (see below in Q13). I don't remember feeling particularly anxious about CAR T or it's uncertainties – I just remember thinking that it was amazing that there was an option for me to potentially be cured of my ALL. I was aware that it was a very new treatment but I have always been a big believer in the power of research and so I trusted my team to help guide me to make the decisions based on what would give me the best chance to become cured and able to move on from this chapter of my life. If anything, it was quite exciting to be a part of something so novel and innovative. I was unaware at the time that this meant I was accessing the treatment via MAA as this was not discussed with me in detail. Therefore I cannot answer some of the questions related to the MAA.

13. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	On the day when I was advised that I had relapsed, my consultant said that there was not enough leukaemia in my flow test for me to be eligible for CAR T at that point (flow showed complete remission but my MRD was 6%). However, the bone marrow results that they had for me were from my biopsy that was taken around 2-3 weeks earlier, so I was advised that I needed to have another biopsy done on that day, as it was likely that my count would be higher by that point. Although this was unexpected and understandably uncomfortable, I knew that this needed to be done with a matter of urgency, so that we could get the results back ready for discussion at the National Panel on the following Friday. Surely enough, my flow cytometry result came back at 16% meaning I could be considered as a candidate for treatment. Time was of the essence in this scenario, and I felt well supported and informed by my clinical team as to why this needed to be done so rapidly to give me the best possible chance of survival.
14. Were patients experiences captured adequately in the MAA tests and assessments? **If not please explain what was missing.**	I don't recall being asked about my experiences specifically in relation to the MAA tests and assessments and therefore cannot offer further insight on this.
15. What outcomes (if any) do you think have not been assessed or captured during the Managed Access period Please tell us why	I don't recall any criteria for the MAA so I am not able to comment on this.
16. Are there any potential equality issues that should be taken into account when considering relapsed or refractory B-cell acute lymphoblastic leukaemia and tisagenlecleucel? Please explain if you think any groups of people with this condition are particularly disadvantage	As mentioned in question 11, CAR T cells are self-derived, meaning there is no need to find a donor or a match. This is an issue that is faced by many patients who are from ethnic minority backgrounds, or those who have mixed heritage, due to the lack of diverse donors on stem cell registries.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	At present, this treatment is the only chance of cure that can be offered to patients with relapsed/refractory ALL. Taking away this option for future patients would disadvantage all patients who find themselves in this scary position and therefore anyone who meets the eligibility criteria should be able to have equal access.
17. Are there any other issues that you would like the committee to consider?	No.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Receiving a diagnosis of relapsed B-ALL had a significant impact on my quality of life, and that of my family too.
- Continued access to innovative treatments is critical for patients with R/R B-ALL as these patients are extremely challenging to treat with very limited treatment options.

- Receiving tisagenlecleucel improved my quality of life substantially and had an overall positive impact on my physical, mental and emotional health - this was a huge advantage when compared to the impacts that my previous treatments had on me, such as my stem cell transplant.
- Tisagenlecleucel is a self-derived cell therapy meaning there is no risk of rejection or GvHD, which is usually a major concern when patients receive allogeneic treatments such as a transplant.
- No other existing treatment currently offer a chance of cure to patients in this position, meaning there is a clear unmet need for this cohort that can be met by allowing continued access to CAR T therapy via the NHS.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory B-cell acute lymphoblastic leukaemia or caring for a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. **Please note that you do not have to answer every question** – they are prompts to guide you.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 2 February 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia

Table 1 About you, relapsed or refractory B-cell acute lymphoblastic leukaemia, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with relapsed or refractory B-cell acute lymphoblastic leukaemia ? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with relapsed or refractory B-cell acute lymphoblastic leukaemia ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory B-cell acute lymphoblastic leukaemia ? **If you are a carer (for someone with relapsed or refractory B-cell acute lymphoblastic leukaemia) please share your experience of caring for them** Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	My son was diagnosed with B-cell ALL shortly before his 17th birthday. He was told that he had an 80% chance of survival through the conventional chemotherapy protocol. This treatment would be intensive at the start, but once through the initial 9 mth period he would be able to participate in most of his school and social life activities, until he had completed the 3 year maintenance phase. He was told from the start that if he relapsed before the end of the 3 year maintenance period, that was a very poor indicator of his treatment being successful in the long term. My son was about to return to start his final year at university without the constraints of being in maintenance, the weekly blood tests, regular bone marrow biopsies under GA and looking forward to being able to socialise the same as other students, return to relationships and his beloved sports that were such a big part of his life. It was one month before the end of his 3+ years of treatment, when he relapsed. He knew, and we knew, that this was not good and he was devastated. We had followed all the maintenance chemotherapy regimens, never missed an appointment or procedure and religiously followed the very restrictive neutropenic protocols; so we knew this was the disease and not any failure by him or us. He was forced into a whole new world of stem cell transplants: the full body radiation preparation (and therefore any chance of any remaining fertility being removed), more full-on chemotherapy, weeks and weeks of isolation in hospital, all assuming a suitable donor could be found. Neither of his two elder siblings were suitable donors, but fortunately a donor was found with 100% match on the AN register. He was quite depressed as he watched his peers leaving home and going

	back to Uni, making plans and moving on with their lives, whilst he sailed into the unknown of 'would his transplant work?' and this dominated every waking minute of his and our lives. No-one would give him any stats for the success rate - he just wanted to know whether what he was about to embark on, was worth it. The focus was all on whether the donor cells would be accepted by his body and whether his new immune system could fight off any albeit small residual, but still detectable, numbers of non CD22 rogue cells. In addition, with absolutely nil neutrophils after the transplant, there was no question of visitors in hospital other than family and this was a very lonely and isolated time from his peers. There wasn't really a choice, because he would die without the treatment and there was nothing else on offer. That's a very big concept to get your head around at any age, but especially one for a young adult who should be in the prime of his life, enjoying adulthood without a care in the world and without the burdens of responsibility that come in later adulthood. Immediately after the actual transplant, he felt well but could not do anything that was part of his normal life: socialising, having a meal at home or going to a restaurant with family or friends, going out to friends' houses, parties, living away from home and participating in Uni life, going on holiday and to festivals. Life was all about being trapped in his hospital room, waiting for the daily blood results to see if any neutrophils had appeared – a sign that the transplant had embedded and his body was responding appropriately. His elder sister had only left one month previously to live in Australia for a year- should she come home and abandon her plans? They were particularly close and he relied heavily on her for emotional support and understanding him on a different level to us as his parents. His elder brother has just returned from university but hadn't got expected grades whilst he floundered feeling helpless from afar. Much of the sibling support fell on him, in his sister's physical absence and this was emotionally extremely hard on him.

7a. What do you think of the current treatments and care available for relapsed or refractory B-cell acute lymphoblastic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. Stem-cell transplantation was nothing short of brutal. The actual procedure itself was not such a big deal, the quality of the treatment and care in the specialist unit was unquestionably the best in the world. But the aftermath was severely challenging, both mentally and physically 7b. My son knew of a few other patients going through the same as him, but one patient was much younger and not used to my son's level of independence from his parents. The other was a little older and had AML but experienced the same frustrations and restrictions on being able to keep up with their friends and participate in 'normal' young adult socialising.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory B-cell acute lymphoblastic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	One of the most over-riding negatives to the transplant was that my son was 20 years old, an adolescent but categorised by the system as an adult. He'd been under the TCT and treated in the dedicated outpatient unit, and on the teenage/young adult wards when he was an inpatient. But that all changed when he relapsed and they moved him to a new consultant and the adult outpatient clinics and inpatient wards. This was disastrous on top of dealing with the recent relapse, poor prognosis, change of all things familiar to him on the wards/TCT outpatients and had a very negative impact on him. We had to beg the head of the nursing service to allow him to be treated by the nurses who had looked after him in TCT outpatients, but they insisted he still be seen by the adult consultants and stayed on the adult wards when inpatient stays were necessary. He was mixing with other, sometimes elderly adult patients who he had nothing whatsoever in common with and without the specialist TCT nurses who understood the particular needs of teenagers/young adults so much more than other nursing staff. Had he not already experienced life on the young adults/TCT wards, he'd have been none the wiser, but this significant change made the whole thing intolerable and couldn't have come at a worse juncture when so much was uncertain and he was desperate to have some stability and continuity with the medical teams that he knew. The aftermath of the transplant severely depleted him physically and mentally. Months and months of isolation from his friends, feeling rubbish from the severe side effects of the radiotherapy and mild GVHD and unable to return to his final year in Uni, or to join in with his peers' social activities, or his sport that he was wedded

	to and the disappointment of cancelled holidays. He had no appetite and lost 30% of his body weight, unable to enjoy his food which usually was a big part of his life. We never got to the bottom of whether this was also a fall-out from the radiotherapy or GCHD in his gut. It felt to us that there was a reticence to treat these symptoms- we were never sure why, but there must have been a medical reason and then talk about insertion of a NG tube. This was perceived by him as another assault on his dignity, however sensitively they tried to put it. Socially, he felt left behind whilst his friends got on with their lives, making plans for their careers or going travelling in gap years. He couldn't make any plans further than a few days ahead and was frustrated when his friends didn't always realise he was either in hospital or trapped at home (which was his safe place), literally sitting by the phone all day waiting to speak to them or possibly have them over for a few hours. When he was finally well enough medically and physically to venture out, after almost 6 months, we (as his parents) were slightly over-protective about his safety and he resented/rejected our offers of transport/ support which led to tensions within the family. He felt like he was being treated as if he were a dependant teenager again, when he was a 20 year old with his own car, who'd already lived away from home at university for 2 years.
9a. If there are advantages of tisagenlecleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	9a. The work-up for my son's CAR-T cells was through an ambulatory infusion of Monoclonal Antibodies (MABs) which had minimal side-effects and, luckily for him, was extremely effective. He reduced the level of disease necessary for there to be enough substrate for the CAR-T cells to be able to 'lock-on' in a matter of weeks and during this time he was living at home, partying, clubbing, going to his best friend's 21st birthday party and giving the speech to the birthday boy! To anyone that didn't know how extremely ill he was on paper, he looked the picture of health. As part of the sign-up to the trial, it was agreed he would be treated back in the TCT unit and have his consultations on the young people's unit, and would only be prevented from being able to stay on the young people's ward if he was an

9c. Does tisagenlecleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	inpatient. For the most part, he was treated as an ambulatory patient, staying at the hospitals pseudo-hotel facility across the road. I think because he felt so well, he enjoyed doing the memory tests looking for any adverse effects to his neurological pathways and being one of the first to have this opportunity of cheating his disease once and for all. So life was very supported with the freedom of not being an inpatient, being able to go out for dinner, have friends to visit him and this was a very big positive - anything was better than the restrictions of being an inpatient. The number of medicines he was on, having achieved full clinical remission (initially), was minimal and another freedom he hadn't enjoyed for many years. He was out playing 5-aside football and rounds of golf with his friends, which would have been unthinkable so soon after his transplant. 9b. His ability to carry on with his life 'as normal' even though in the middle of treatment, being able to live in the hospital's hotel as an ambulatory patient. 9c. He avoided all the gruesome side-effects of chemotherapy, hair loss, nausea and vomiting, neutropenia, low platelets and anaemia, and GVHD. He would not have had to face the issues of infertility or contemplated other such thoughts that would never normally cross the mind of healthy young adults of his age.
10. If there are disadvantages of tisagenlecleucel over current treatments on the NHS please describe these. For example, are there any risks with tisagenlecleucel? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	The uncertainty of the success and lack of expertise as to the factors that might increase the success rate or put him at an advantage/ disadvantage of achieving successful remission. How much residual disease prior to commencement of treatment was optimal? How much expansion was 'good'? He suffered from a cytokine storm and ended up in intensive care for several days with lots of unanswered questions as to what to do for the best, because this was the first trial in the UK. Would the reversal drug undermine the efficacy of the treatment?
11. Are there any groups of patients who might benefit more from tisagenlecleucel or any who may benefit less? If so, please describe them and explain why	I think it could be particularly beneficial for young adults who wouldn't normally be facing existential thoughts, having to consider their long-term fertility, don't want anything other than to be 'normal', to be able to get on with their school/uni/work/social life and make plans for the future. By allowing the social

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	support structures to remain intact, mental well-being can be maintained for both the patient and the wider family (siblings and parents) who are also often forgotten as collateral victims of this cruel disease. Whilst patients must rely on a donor, those for whom it's difficult to find a suitable donor on the register, may struggle more. I can't comment on patients with other health issues as I don't have experience of this.
12. If you have experience of this treatment during the period of Managed Access please tell us your views on the results from tests and assessments that have been used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	When my son presented with symptoms that suggested possible relapse after his stem cell transplant, he had a Bone Marrow biopsy to confirm the findings. The clinical team presented the adverse results and within minutes were talking about the possibility of CAR-T cell trials. They were very excited about being able to offer this to him, enthusiastic about this cutting edge treatment and the potential for a cure. They were currently recruiting for a trial and had already done their homework and knew that he fitted their criteria. The only questions that were relevant to his acceptance on the trial were whether he was willing to sign up and whether his stem cell donor would be willing to donate again. Thankfully the donor was willing, but that was another period of uncertainty whilst we awaited the donor's decision. The question of choice and consents etc was academic- the question that would have been better put was 'do you want to have a last stab at a cure or die'? We had nothing else. The question about the cause of the ultimate failure of CAR-T cell therapy has been shown from subsequent trials to be associated with the MAB used for his induction which negatively impacted the outcome. They could not have known this at the time.
13. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Not that I remember

14. Were patients experiences captured adequately in the MAA tests and assessments? **If not please explain what was missing.**	This was very early days in CAR-T trials (August 2017). So many things were uncertain and the anecdotal experiences of previous patients were sparse – very few patients were around to ask about their experiences and how things went for them. This will have now changed, of course, with the passage of time and multiple trials to refer to.
15. What outcomes (if any) do you think have not been assessed or captured during the Managed Access period Please tell us why	No-one asked him to complete any sort of questionnaire about the experience, either during or after the treatment. Maybe they wanted to concentrate on objective assessments rather than subjective feelings of the patients.
16. Are there any potential equality issues that should be taken into account when considering relapsed or refractory B-cell acute lymphoblastic leukaemia and tisagenlecleucel? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Depending whether the patients are relying on a donor or using their own T-cells, there could be issues over the availability of a suitable donor or, as was in my son's case, having to go back to the original donor and ask again. By definition that means that the donor's first donated cells were not successful. This could be a very tricky situation to negotiate and quite a lot of renewed pressure on the donor. Suitable donors for some of the patients, particularly with mixed race parents are poorly represented on the register. The potential for off-the-shelf, generic CAR-T cells would be of considerable advantage and would negate the need for a suitable donor and the delays caused by the laboratory time to manufacture the CAR-T cells.

17. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Teenagers/young adults want nothing more than to continue to be part of their peer group as much as possible during their treatment: socialising and doing whatever their peers are doing, be it being at school, going on to University or getting an apprenticeship/starting work.
- The aftermath of Stem Cell Transplants is brutal physically and emotionally, with the certainty of infertility.
- For those patients aged 18-20 years, who crave the familiarity of the clinical professionals from their previous conventional treatment but find themselves in their darkest moments of relapse, in the no-man's land between TCT outpatient units/ inpatient wards and being treated as adult outpatient/inpatients; that's not a good time to take away everything that is familiar to them.
- The experience of the prior work-up, during and post CAR-T cell therapy was as near to being normal as was possible, for such a desperately sick young man.
- The ability to avoid being an inpatient and be treated in ambulatory care, whilst staying at the hospital's pseudo hotel facility, was transformative to his wellbeing.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]

External Assessment Group Report

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, Division of Population Health, University of Sheffield, UK
	Katy Cooper, Senior Research Fellow, SCHARR, Division of Population Health, University of Sheffield, Sheffield, UK
	Sarah Ren, Research Associate, SCHARR, Division of Population Health, University of Sheffield, Sheffield, UK
	Mon Mon Yee, Research Assistant, SCHARR, Division of Population Health, University of Sheffield, Sheffield, UK
	Mark Clowes, Information Specialist, SCHARR, Division of Population Health, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	22nd December 2023 (post-FAC version)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136153.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Dr John Moppett, University Hospitals Bristol NHS Foundation Trust, Professor Adele Fielding, University College London Hospitals NHS Foundation Trust, and Professor Rachael Hough, University College London Hospitals NHS Foundation Trust, for clinical advice relating to this project. We also thank Dr Sunhong Kwon and Dr Kate Ren, SCHARR, for providing comments on the draft report and Mrs Gill Rooney, Programme Manager, SCHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tappenden P, Cooper K, Ren S, Yee M, Clowes M. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]: External Assessment Group Report. Sheffield Centre for Health and Related Research (SCHARR), 2023.

Contributions of authors

Paul Tappenden led the assessment. Mark Clowes critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Sarah Ren critiqued the statistical aspects of the submission. Mon Mon Yee and Paul Tappenden critiqued the health economic analysis submitted by the company and conducted additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF BOXES

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
AIEOP	Associazione Italiana di Ematologia e Oncologia Pediatrica
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogenic stem cell transplantation
AML	Acute myeloid leukaemia
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
ATMP	Advanced therapy medicinal products
AUC	Area under the curve
BCR-ABL	Breakpoint cluster region-Abelson
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best Overall Response
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CCLG	Children's Cancer and Leukaemia Group
CD-19	Cluster of differentiation 19
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEC	Clofarabine, etoposide and cyclophosphamide
CHRI	Child Health Rating Inventory
CI	Confidence interval
CMU	Commercial Medicines Unit
CNS	Central nervous system
CR	Complete remission
CRD	Centre for Reviews and Dissemination
CRi	Complete remission with incomplete blood count recovery
CRS	Cytokine release syndrome
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DFCI	Dana Farber Cancer Institute
DLBCL	Adult diffuse large B-cell lymphoma
DM	Disease modifier
DoR	Duration of remission
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis

EAG	External Assessment Group
ECG	Electrocardiogram
EF	Event-free
EFS	Event-free survival
eMIT	Electronic Market Information Tool
EQ-5D	Euroqol 5-Dimensions
EQ-5D-3L	Euroqol 5-Dimensions 3-Levels
EQ-5D-Y	Euroqol 5-Dimensions Youth
EQ-VAS	Euroqol Visual Analogue Scale
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
ESS	Effective sample size
EU	European Union
FAS	Full analysis set
FL	Follicular lymphoma
FLAG-IDA	Fludarabine, cytarabine, G-CSF and idarubicin
FU	Follow-up
G-CSF	Granulocyte-colony stimulating factor
GEE	Generalised estimating equation
GRACE	Good Research for Comparative Effectiveness
GVHD	Graft versus host disease
HAS	Haute Autorité de Santé
HES	Hospital Episode Statistics
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HTA	Health Technology Assessment
HUI-2	Health Utilities Index Mark 2
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
KM	Kaplan-Meier
LFT	Liver function test
LYG	Life year gained
MA	Managed access
MAIC	Matching-adjusted indirect comparison
MCM	Mixture-cure model
MEDLINE	Medical Literature Analysis and Retrieval System Online

MLL	Mixed-lineage leukaemia
MRD	Minimal residual disease
N/a	Not applicable
NCCN	National Comprehensive Cancer Network
NDRS	National Disease Registration Service
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NOMA	Norwegian Medicines Agency
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NR	Not reported
NSSG	NHS Network Site Specific Group
ONS	Office for National Statistics
ORR	Overall remission rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PedsQL	Paediatric quality of life
PFS	Progression-free survival
Ph+ve	Philadelphia chromosome-positive
Ph-ve	Philadelphia chromosome-negative
PROs	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
R/R	Relapsed or refractory
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RD	Relapsed disease
RFS	Relapse-free survival
ROBINS-I	Risk Of Bias In Non-randomised Studies - Interventions
SACT	Systematic Anti-Cancer Therapy
SAE	Serious adverse event
SCIg	Subcutaneous immunoglobulin
SCT	Stem cell transplantation
SD	Standard deviation
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
STA	Single Technology Appraisal
TA	Technology Appraisal
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document

TTO	Time trade-off
VAS	Visual analogue scale
VOD	Veno-occlusive disease
VXLD	Vincristine, dexamethasone, pegylated asparaginase, and doxorubicin
WHO	World Health Organization
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses tisagenlecleucel for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) which is refractory, in relapse post-transplant, or in second or later relapse. This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the EAG's preferred analysis and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are detailed in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6290	Summary of issue	Report sections
Issue 1	Use of ELIANA data in preference to the pooled tisagenlecleucel dataset	5.3.5 (critical appraisal point 2)
Issue 2	EFS definition in the tisagenlecleucel studies may exaggerate benefits	5.3.5 (critical appraisal point 3)
Issue 3	Uncertainty around relative effectiveness of tisagenlecleucel versus comparators	5.3.5 (critical appraisal point 5)
Issue 4	Issues relating to the health state utility values	5.3.5 (critical appraisal point 8)
Issue 5	Uncertainty around IVIg treatment duration for patients with hypogammaglobulinaemia	5.3.5 (critical appraisal point 9)

Allo-SCT - allogeneic stem cell transplantation; EFS - event-free survival; IVIg - intravenous immunoglobulin

There are three key differences between the company's original base case analysis and the EAG's preferred analysis:

(i) *Pooled tisagenlecleucel dataset*. The company's base case model uses mixture-cure models (MCMs) fitted to data on event-free survival (EFS) and overall survival (OS) from the ELIANA data (data cut-off [DCO] November 2022) for patients who receive the tisagenlecleucel infusion. The EAG's preferred analysis uses MCMs for EFS and OS based on the pooled dataset of ELIANA, ENSIGN and B2101J, including the latest data cut-off for each study.

(ii) *Relative effectiveness of tisagenlecleucel versus comparators.* The company's base case model uses von Stackelberg *et al.* as the source of OS and the allogeneic stem cell transplantation (allo-SCT) rate for blinatumomab, and Jeha *et al.* as the source of OS and the allo-SCT rate for FLAG-IDA (fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor [G-CSF]). The EAG's preferred analysis uses OS data and allo-SCT rates from the RIALTO study for blinatumomab and from Kuhlen *et al.* for FLAG-IDA.

(iii) *Uncertainty around intravenous immunoglobulin (IVIg) treatment duration.* The company's model assumes that patients who require IVIg will receive treatment for 11.4 months, based on the median time to B-cell recovery in the 2017 data-cut of ELIANA. The EAG's preferred analysis assumes that the mean treatment duration per patient requiring IVIg is equivalent to the 5-year restricted mean EFS based on the pooled dataset (mean duration = 25.5 months). These durations are applied to 30.4% of patients in the model.

The EAG's model also includes other minor amendments including the correction of model errors, the inclusion of terminal care costs for patients who die prior to receiving the tisagenlecleucel infusion and updated drug acquisition costs.

1.2 Overview of key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with blinatumomab and FLAG-IDA, tisagenlecleucel is assumed to impact on QALYs by:

- Extending EFS
- Extending OS
- Increasing the frequency of adverse events (AEs), particularly cytokine release syndrome (CRS) and infections, which leads to greater QALY losses compared with the comparators.

Compared with blinatumomab and FLAG-IDA, tisagenlecleucel is assumed to affect costs by:

- Increasing overall costs due to the acquisition cost of tisagenlecleucel and additional pre-treatments
- Increasing overall disease management costs due to extended OS
- Impacting on the costs associated with subsequent allo-SCT, with a higher rate for tisagenlecleucel versus FLAG-IDA (in the company's base case only) but a lower rate for tisagenlecleucel versus blinatumomab, and
- Increasing the costs associated with managing AEs, particularly B-cell aplasia.

The modelling assumptions that have the greatest effect on the ICER for tisagenlecleucel versus its comparators are:

- The choice of dataset used to inform outcomes for patients receiving the tisagenlecleucel infusion (ELIANA only versus pooled dataset). The choice of MCM for OS is highly influential.
- The choice of study used to inform outcomes for blinatumomab (von Stackelberg *et al.* versus RIALTO) and FLAG-IDA (Jeha *et al.* versus Kuhlen *et al.*). For blinatumomab, the choice of MCM for OS is also important.
- The health state utility values (Kelly *et al.* versus ELIANA).
- The duration of IVIg required to treat hypogammaglobulinaemia.
- The decision modifier and the application of non-reference case discount rates of 1.5%.

1.3 The decision problem: Summary of the EAG's key issues

In NICE Technology Appraisal (TA) 554, tisagenlecleucel was recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed or refractory (R/R) B-cell ALL in people aged up to 25 years. With the exception of TA554, current NICE recommendations for R/R B-cell ALL have been limited to therapies which are licensed only for the treatment of adult patients. In TA450, blinatumomab was recommended as an option for treating Philadelphia-chromosome-negative (Ph-ve) R/R precursor B-cell ALL in adults. In 2018, the European marketing authorisation for blinatumomab was expanded to include paediatric patients aged 1 year or older. In TA541, inotuzumab ozogamicin was recommended as an option for treating R/R CD-22-positive B-cell precursor ALL in adults. In TA893, brexucabtagene autoleucel was recommended for use within the CDF as an option for treating R/R B-cell ALL in people aged 26 years and over.

The company's proposed positioning of tisagenlecleucel is in line with its full licensed indication, that is, for paediatric and young adult 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 decision problem addressed in the company's submission (CS) is partly in line with the final NICE scope. The CS excludes several comparators listed in the NICE scope - inotuzumab ozogamicin, tyrosine kinase inhibitors (TKIs), stem cell transplantation (SCT) and best supportive care (BSC).

Regarding the assumed salvage chemotherapy regimens, the EAG's clinical advisors commented that NOPHO blocks may also be used instead of FLAG-IDA. The advisors also noted that inotuzumab ozogamicin is used off-label in children. The advisors further commented that blinatumomab is likely to be the main comparator for tisagenlecleucel, and that salvage chemotherapy would only be used in patients for whom blinatumomab is not suitable.

1.4 The clinical effectiveness evidence: Summary of the EAG's key issues

The CS presents data on three single-arm studies of tisagenlecleucel (ELIANA, ENSIGN and B2101J) in a total of 200 patients aged up to 25 years with B-cell ALL that is refractory, in relapse post-SCT, in second or later relapse, or ineligible for SCT. In addition, the National Health Service England (NHSE) Systematic Anti-Cancer Therapy (SACT) dataset provides data on 121 patients receiving tisagenlecleucel in England during the managed access period. Across the three pooled clinical studies, 57% of patients had prior SCT. The proportion receiving subsequent allo-SCT was 23% in ELIANA, 14% in ENSIGN and 14% in B2101J (18% pooled across studies), while the proportion in the NHSE dataset was reported as 11% (though the EAG questioned the reliability of this estimate). Median EFS was 21 months across the three pooled clinical studies. Median OS was 48 months across the three pooled studies, while in the NHSE dataset, median OS was not reached (3-year OS was 67%). Frequent AEs included CRS (81%), hypogammaglobulinaemia (51%) and decreases in white blood cells (57%), neutrophils (52%) and platelets (47%). In ELIANA, 3/79 (3.8%) deaths were reported as being potentially related to tisagenlecleucel infusion (intracranial haemorrhage, systemic mycosis and viral encephalitis), while no deaths related to tisagenlecleucel were reported in ENSIGN or B2101J.

The company conducted a matching-adjusted indirect comparison (MAIC) for OS. The company preferred to include only the ELIANA study for tisagenlecleucel, while the EAG considers that, given the similarities in design and populations, the pooled dataset including all three studies (N=200) should be used in the MAIC. The MAIC included two comparators: blinatumomab and salvage chemotherapy. For blinatumomab, the company used a single-arm study of 70 patients by von Stackelberg *et al.,* 2016 (subsequent allo-SCT rate 34%; median OS 7.5 months). For salvage chemotherapy, the company used a single-arm study of 61 patients by Jeha *et al.*, 2006 (subsequent allo-SCT rate 15%; median OS 3 months). The MAIC for tisagenlecleucel vs. blinatumomab gave a hazard ratio (HR) for OS of 0.32 (95% confidence interval [CI] 0.21 to 0.48, $p<0.001$), while the MAIC for tisagenlecleucel vs. salvage chemotherapy gave an HR for OS of 0.20 (95% CI 0.14 to 0.31, $p<0.001$). The EAG has concerns that the company's selection of comparator studies was not transparent, that rates of subsequent allo-SCT in the selected comparator studies were lower than expected, and that not all relevant prognostic factors and treatment effect modifiers were included and properly adjusted for. These issues are discussed further in Section 1.5. The EAG's clinical advisors suggested that the RIALTO study (subsequent allo-SCT rate 53%; median OS 14.6 months) may better reflect outcomes for patients receiving blinatumomab. For salvage chemotherapy, one of the EAG's clinical advisors suggested that the study by Kuhlen *et al*., 2018 (subsequent allo-SCT rate 26%; median OS 6 months) may better reflect outcomes for FLAG-IDA, while another clinical advisor suggested that OS for FLAG-IDA may lie somewhere between the estimates reported by Jeha *et al.* and Kuhlen *et al.*

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company's model assesses the cost-effectiveness of tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA for the treatment of paediatric and young adult patients with R/R B-cell ALL. The model uses a partitioned survival model approach for patients receiving treatment, with a preceding decision tree which is used to account for costs and outcomes accrued by patients for whom tisagenlecleucel is planned but not received (due to AEs, manufacturing error or early death). The partitioned survival model includes three health states: (i) event-free (EF), (ii) relapsed/progressed disease (PD), and (iii) dead. The model evaluates the cost-effectiveness of tisagenlecleucel versus its comparators from an NHS and Personal Social Services (PSS) perspective over an 88-year (lifetime) horizon. Caregiver effects are not included. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis.

For tisagenlecleucel, EFS and OS are modelled using MCMs fitted to data from ELIANA. For blinatumomab and FLAG-IDA, OS is modelled using MCMs fitted to data from von Stackelberg *et al.* and Jeha *et al*., respectively. Allo-SCT rates for each treatment group are taken from these same sources. Health state utility values are based on external literature (Kelly *et al.*), rather than the Euroqol 5-Dimensions (EQ-5D) data collected in ELIANA. The model assumes that the HRQoL of patients who remain alive after 5 years is equivalent to that of patients who are event-free prior to this timepoint. Follow-up costs are minimal after 5-years. The model includes costs associated with: (i) pre-treatment administered prior to tisagenlecleucel infusion, including leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy (in the tisagenlecleucel group only), (ii) treatment, including procedure/drug acquisition costs, administration costs and hospitalisation costs; (iii) health state resource use; (iv) the management of AEs, including short-term events and B-cell aplasia which may persist in the longer-term; (v) subsequent allo-SCT, and (vi) terminal care. For patients who receive the tisagenlecleucel infusion, the base case model applies NHSE chimeric antigen receptor T-cell (CAR-T) therapy tariff costs which covers the costs of leukapheresis, CAR-T administration, AEs, monitoring and training incurred in the first 100 days following the CAR-T infusion. Resource use and cost parameters are based on ELIANA, the NHSE CAR-T tariff, published literature, standard costing sources and clinical assumptions. Cost-effectiveness results are reported as pairwise comparisons; a full incremental analysis is not presented in the CS.

A Patient Access Scheme (PAS) is available for tisagenlecleucel which takes the form of a simple price discount of [redacted]. All results presented in this EAG report include this PAS. Excluding QALY weighting, the probabilistic version of the company's original model suggests that compared with blinatumomab, tisagenlecleucel generates an additional [redacted] QALYs at an additional cost of [redacted]. For the comparison against FLAG-IDA, the model suggests that tisagenlecleucel generates an additional [redacted] QALYs at an additional cost of [redacted]. The corresponding probabilistic ICERs for tisagenlecleucel

versus blinatumomab and FLAG-IDA are £20,410 per QALY gained and £30,031 per QALY gained, respectively. The deterministic ICERs are similar. The company's QALY shortfall calculations suggest a decision modifier of 1.7 for both comparisons. When QALY weighting is included, the probabilistic ICERs for tisagenlecleucel versus blinatumomab and FLAG-IDA are estimated to be £12,006 and £17,665 per QALY gained, respectively.

Following the clarification process, the company submitted two revised versions of the economic model which included minor error corrections and additional functionality. The company's revised model results are similar to their original model results.

The EAG has five key concerns regarding the company's model. These relate to: the dataset used to model outcomes for tisagenlecleucel-treated patients (Issue 1); the potential exaggeration of EFS benefits in the tisagenlecleucel group (Issue 2); uncertainty around the relative effectiveness of tisagenlecleucel versus its comparators (Issue 3); the use of utility values which do not adhere to the NICE Reference Case (Issue 4), and uncertainty surrounding the duration of IVIg treatment for hypogammaglobulinaemia (Issue 5). These issues are summarised below. All ICERs reported below include the correction of model errors by the EAG.

Issue 1: Use of ELIANA data in preference to the pooled tisagenlecleucel dataset

Report section	5.3.5 (Critical appraisal point 2)
Description of issue and why the EAG has identified it as important	The clinical section of the CS includes analyses of tisagenlecleucel based on a pooled dataset including ELIANA, ENSIGN and B2101J. However, the company's economic model is informed by data from ELIANA only, based on the latest DCO (November 2022). Whilst patients enrolled in ENSIGN and B2101J had similar characteristics to those in ELIANA, these data are not used in the economic model. This substantially reduces the sample size and excludes relevant data (ELIANA only N=79; pooled dataset N=200). TA554 was based on analyses of the pooled dataset. All previous economic analyses of tisagenlecleucel included in the company's systematic literature review (SLR) used a pooled dataset including ELIANA and ENSIGN, with most analyses also including B2101J.
What alternative approach has the EAG suggested?	The pooled tisagenlecleucel dataset suggests less favourable EFS and OS compared with ELIANA alone. The EAG believes that the economic model should be informed by the pooled dataset. This includes data on EFS, OS, the allo-SCT rate and AE frequency.
What is the expected effect on the cost-effectiveness estimates?	For tisagenlecleucel versus blinatumomab, the QALY-weighted ICER based on the pooled dataset is estimated to be £13,395 per QALY gained. For tisagenlecleucel versus FLAG-IDA, the equivalent ICER is estimated to be £21,747 per QALY gained (EA2). These analyses each apply a log-logistic MCM for OS and a Gompertz MCM for EFS in the tisagenlecleucel group. They also apply the pooled SCT rate and AE frequency data.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further evidence or analyses are required to resolve this issue.

Issue 2: EFS definition in the tisagenlecleucel studies may exaggerate benefits

Report section	5.3.5 (Critical appraisal point 3)
Description of issue and why the EAG has identified it as important	The definition of EFS in the tisagenlecleucel studies includes censoring for allo-SCT and further therapy, and excludes other clinically relevant events such as minimal residual disease (MRD) relapse and loss of B-cell aplasia. The EAG's clinical advisors raised concerns that the definition of EFS and censoring approach used in the tisagenlecleucel studies may exaggerate the benefits of this treatment. The advisors highlighted a recent national UK analysis of real-world outcomes for 128 children and young adults who received tisagenlecleucel which reported markedly shorter median EFS when the definition included molecular or frank relapse, further therapy, death or treatment failure (ELIANA EFS definition – 22 months; stringent EFS definition –7 months). Had a more stringent definition of EFS been used in the tisagenlecleucel studies, the EAG expects that the mean EFS estimates would be lower than those estimated by the company's model.
What alternative approach has the EAG suggested?	The EAG believes that the company could have presented sensitivity analyses using EFS without censoring for allo-SCT or further therapy. However, this would not fully address the EAG's advisors' concerns regarding the definition of EFS used in the tisagenlecleucel studies.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is not fully clear. As a consequence of this issue, the model results presented by the company and the EAG might be optimistic.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 3: Uncertainty around relative effectiveness of tisagenlecleucel versus comparators

Report section	5.3.5 (Critical appraisal point 5)
Description of issue and why the EAG has identified it as important	The EAG believes that there is substantial uncertainty surrounding the relative effectiveness of tisagenlecleucel versus its comparators. The key factors contributing to this uncertainty are summarised below: • The available evidence for tisagenlecleucel and its comparators is limited to single-arm studies. • The company has selected studies to represent outcomes for blinatumomab and FLAG-IDA in which allo-SCT rates were lower and OS outcomes were poorer than would be expected in patients who would otherwise be eligible for tisagenlecleucel in clinical practice. • The company has undertaken unanchored MAICs. Unanchored MAICs rely on the assumption that all potential prognostic factors and treatment effect modifiers have been included in the adjustment model. This is unlikely to be the case. The MAIC-adjusted OS is very similar to the unadjusted OS. • The company's base case economic analyses rely on naïve indirect comparisons. These analyses assume that the distributions of all prognostic factors and treatment effect modifiers are equivalent between the studies. This assumption is also unlikely to be reasonable. • There remains uncertainty around the long-term outcomes for patients treated with tisagenlecleucel. The economic model is sensitive to the choice of OS function for tisagenlecleucel and blinatumomab.

What alternative approach has the EAG suggested?	The EAG disagrees with the company's choice of comparator study for both blinatumomab and FLAG-IDA. The EAG's clinical advisors suggested that RIALTO may better reflect allo-SCT rates and OS outcomes expected with blinatumomab in clinical practice. For FLAG-IDA, one of the EAG's clinical advisors suggested that Kuhlen *et al*. would better reflect outcomes expected in practice, while another clinical advisor suggested that OS for FLAG-IDA may lie somewhere between the estimates reported by Jeha *et al.* and Kuhlen *et al.*
What is the expected effect on the cost-effectiveness estimates?	For tisagenlecleucel versus blinatumomab, the QALY-weighted ICER including the pooled dataset for tisagenlecleucel and the RIALTO study for blinatumomab is estimated to be £32,568 per QALY gained (EA3). The EAG notes that using RIALTO reduces the decision modifier for the comparison against blinatumomab from 1.7 to 1.2. For tisagenlecleucel versus FLAG-IDA, the QALY-weighted ICER using the pooled dataset for tisagenlecleucel and Kuhlen *et al.* as the source of comparator data is estimated to be £25,829 per QALY gained. One of the EAG's clinical advisors preferred the use of the exponential MCM for OS in the tisagenlecleucel group; this analysis suggests a lower QALY-weighted ICER for tisagenlecleucel versus blinatumomab of £25,836 per QALY gained (ASA2a). Applying the less optimistic exponential MCM to the RIALTO data reduces the QALY weighted ICER for tisagenlecleucel versus blinatumomab to £17,898 per QALY gained (ASA1c). This is because the decision modifier increases from 1.2 to 1.7.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input around the selection of preferred MCMs based on the alternative sources of comparator data may be warranted.

Issue 4: Issues relating to the health state utility values

Report section	5.3.5 (Critical appraisal point 8)
Description of issue and why the EAG has identified it as important	The utility values for the event-free (EF) and progressed disease (PD) states in the company's model are based on a previous modelling study reported by Kelly *et al.* The EF utility value has been estimated using Short Form 36 (SF-36) scores mapped to the Health Utilities Index Mark 2 (HUI-2). The PD utility value is based on Child Health Rating Inventory (CHRI) data mapped to the EQ-5D. These values were also applied in the model used to inform NICE TA554. The utility values applied in the model are not fully in line with the NICE Reference Case. EQ-5D-3L data are available from patients in ELIANA, but are limited by their small sample size (N=61). The ELIANA EQ-5D-3L data are included in sensitivity analyses presented by the company and the EAG. No other relevant EQ-5D estimates were identified from the company's SLR of HRQoL studies.
What alternative approach has the EAG suggested?	The EAG believes that the choice of relevant studies is limited to Kelly *et al.* and ELIANA. Both studies have been included in the economic analyses conducted by the company and the EAG.
What is the expected effect on the cost-effectiveness estimates?	Starting from the EAG's preferred analysis of tisagenlecleucel versus blinatumomab (EA7a), including utility values from ELIANA (ASA6) decreases the QALY-weighted ICER from £35,332 to £27,482 per QALY gained: the QALY-weighted ICER is reduced because the disease modifier increases from 1.2 to 1.7. For the comparison of tisagenlecleucel versus FLAG-IDA, the equivalent analysis increases the QALY-weighted ICER from £26,845 to £29,791 per QALY gained.

What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required. However, the EAG believes that neither source of utility values is ideal and both studies are relevant for consideration.

Issue 5: Uncertainty around IVIg treatment duration for patients with hypogammaglobulinaemia

Report section	5.3.5 (Critical appraisal point 9)
Description of issue and why the EAG has identified it as important	In TA554, the Evidence Review Group (ERG) highlighted uncertainty around which patients would require IVIg replacement therapy and the duration over which treatment would be required. The company's model assumes that 30.4% of all patients receiving the tisagenlecleucel infusion will receive IVIg treatment (75% of those patients with hypogammaglobulinemia in ELIANA). These patients are assumed to require treatment for 11.4 months, based on the median time to B-cell recovery in the 2017 data-cut of ELIANA. The more recent 2022 data-cut of ELIANA suggests that median time to B-cell recovery was 38.6 months, which is substantially longer than the company's estimate. Clinical expert feedback received by the company suggested that 38.6 months was a much longer duration of treatment than would be expected in clinical practice. The EAG's clinical advisors commented that patients with hypogammaglobulinaemia may require IVIg treatment continuously until loss of B-cell aplasia (which indicates loss of persistence to tisagenlecleucel) or until they undergo allo-SCT. One clinical advisor suggested that a reasonable estimate of the mean duration would involve estimating the area under the EFS function, considering a maximum duration of 5 years. Additional data provided in an addendum to the NHSE SACT report suggest that 47% of patients who received the tisagenlecleucel infusion received IVIg therapy. The NHSE report states that the mean time to discontinuation of IVIg was 13.3 months, although the EAG believes that this reflects a crude mean of event and censoring times; this approach does not handle censoring appropriately. Based on the area under the curve (AUC) for time to treatment discontinuation for these patients, the estimated mean treatment duration was approximately 18 months. Data provided in the NHSE report indicate that many patients receiving IVIg were censored with less than 12 months follow-up.
What alternative approach has the EAG suggested?	The EAG believes that the company's model underestimates the net costs of IVIg treatment per patient receiving the tisagenlecleucel infusion. • The company's revised model suggests that the total IVIg cost per patient receiving the tisagenlecleucel infusion is £6,174. • Based on a 5-year restricted mean AUC estimate of EFS for the pooled dataset (25.5 months applied to 30.4% of all patients), the EAG's estimated total IVIg cost per patient receiving the tisagenlecleucel infusion is £13,809. • Based on the SACT data, 47% of patients receive IVIg for a mean duration of 18 months, resulting in a total IVIg cost per patient receiving tisagenlecleucel of £15,081. This is similar to the EAG's estimate.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's preferred comparison of tisagenlecleucel versus blinatumomab, the QALY-weighted ICER is estimated to be £35,332 per QALY gained (EA7a). Applying the company's lower cost of IVIg reduces the ICER to £32,957 per QALY gained. Based on the EAG's preferred comparison of tisagenlecleucel versus FLAG-IDA, the QALY-weighted ICER is estimated to be £26,845 per QALY gained (EA7a). Applying the company's lower cost of IVIg reduces the ICER to £26,013 per QALY gained.

	Applying the NHSE SACT data on IVIg use results in ICERs which are very similar to the EAG's preferred estimates (ASA10a). Assuming a longer duration of IVIg treatment has the propensity to result in considerably less favourable ICERs for tisagenlecleucel (ASA10c).
What additional evidence or analyses might help to resolve this key issue?	The SACT data have reduced uncertainty around IVIg costs. Further clinical input around the maximum duration of IVIg treatment may be useful.

1.6 Summary of EAG's preferred model and sensitivity analysis results

The results of the EAG's preferred model are summarised in Table 2. EA7 reflects the EAG's preferred model; results are presented separately using the probabilistic and deterministic versions of the model (EA7b and EA7a, respectively). Additional sensitivity analyses (ASAs) are presented in Table 3; these analyses use the EAG's preferred deterministic model (EA7a) as a starting point.

Modelling errors identified by the EAG are described in Section 5.3.5. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 5.5.

Table 2: EAG's preferred model results

Scenario	Tisagenlecleucel vs blinatumomab					Tisagenlecleucel vs FLAG-IDA				
	DM	Inc. QALYs	Inc. Costs	ICER excl. QALY weighting	ICER incl. QALY weighting	DM	Inc. QALYs	Inc. Costs	ICER excl. QALY weighting	ICER incl. QALY weighting
Company's original base case model										
Company's original base case, deterministic	1.7	[redacted]	[redacted]	**£19,218**	**£11,304**	1.7	[redacted]	[redacted]	**£30,778**	**£18,105**
Company's original base case, probabilistic	1.7	[redacted]	[redacted]	**£20,410**	**£12,006**	1.7	[redacted]	[redacted]	**£30,031**	**£17,665**
EAG's preferred analysis										
EA1: Correction of model errors	1.7	[redacted]	[redacted]	£18,909	£11,123	1.7	[redacted]	[redacted]	£30,833	£18,137
EA2: Pooled tisagenlecleucel dataset, OS=log-logistic, EFS=Gompertz, plus pooled SCT rate and AE rates	1.7	[redacted]	[redacted]	£22,771	£13,395	1.7	[redacted]	[redacted]	£36,970	£21,747
EA3: Alternative comparator studies and models: RIALTO blinatumomab, OS=log-logistic MCM, EFS=HR applied to OS model, allo-SCT rate=53% Kuhlen chemotherapy, OS=log-normal MCM, EFS=HR applied to OS model, allo-SCT rate=26%	1.2	[redacted]	[redacted]	£39,082	£32,568	1.7	[redacted]	[redacted]	£43,910	£25,829
EA4: Inclusion of terminal care costs for patients dying prior to receiving the infusion	1.2	[redacted]	[redacted]	£39,518	£36,592	1.7	[redacted]	[redacted]	£44,127	£25,957
EA5: IVIg treatment duration = 25.5 months	1.2	[redacted]	[redacted]	£42,368	£35,307	1.7	[redacted]	[redacted]	£45,541	£26,789
EA6: Inclusion of updated unit costs from eMIT and BNF	1.2	[redacted]	[redacted]	£42,398	£35,332	1.7	[redacted]	[redacted]	£45,636	£26,845
EA7a: EAG-preferred model (EA1-6 combined), deterministic	1.2	[redacted]	[redacted]	**£42,398**	**£35,332**	1.7	[redacted]	[redacted]	**£45,636**	**£26,845**
EA7b: preferred model (EA1-6 combined), probabilistic	1.2	[redacted]	[redacted]	**£45,052**	**£37,543**	1.7	[redacted]	[redacted]	**£43,947**	**£25,851**

EA - exploratory analysis; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; OS - overall survival; EFS - event-free survival; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; DM - decision modifier; SCT - stem cell transplantation; HR - hazard ratio; MCM - mixture-cure model; eMIT - electronic Market Information Tool; BNF - British National Formulary

Table 3: EAG's additional sensitivity analysis results

Scenario	Tisagenlecleucel vs blinatumomab					Tisagenlecleucel vs FLAG-IDA				
	DM	Inc. QALYs	Inc. Costs	ICER excl. QALY weighting	ICER incl. QALY weighting	DM	Inc. QALYs	Inc. Costs	ICER excl. QALY weighting	ICER incl. QALY weighting
ASA1a - Blin - von Stackelberg *et al.* (OS=log-normal)	1.7	[redacted]	[redacted]	£24,060	£14,153	1.7	[redacted]	[redacted]	£47,039	£27,670
ASA1b - FLAG-IDA = Jeha *et al.* (OS=log-normal)	1.2	[redacted]	[redacted]	£43,618	£36,349	1.7	[redacted]	[redacted]	£37,501	£22,059
ASA1c - Blinatumomab = RIALTO (OS=exp. MCM)	1.7	[redacted]	[redacted]	£30,426	£17,898	1.7	[redacted]	[redacted]	£46,176	£27,162
ASA1d - FLAG-IDA = average of Jeha and Kuhlen	1.2	[redacted]	[redacted]	£43,265	£36,054	1.7	[redacted]	[redacted]	£39,161	£23,036
ASA2a - Tisagen OS: MCM exponential	1.2	[redacted]	[redacted]	£31,003	£25,836	1.7	[redacted]	[redacted]	£38,579	£22,694
ASA2b - Tisagen OS: MCM Weibull	1.2	[redacted]	[redacted]	£32,066	£26,721	1.7	[redacted]	[redacted]	£39,332	£23,136
ASA2c - Tisagen OS: MCM Gompertz	1.2	[redacted]	[redacted]	£35,559	£29,633	1.7	[redacted]	[redacted]	£41,655	£24,503
ASA2d - Tisagen OS: MCM log-normal	1.2	[redacted]	[redacted]	£58,712	£48,927	1.7	[redacted]	[redacted]	£52,929	£31,135
ASA2e - Tisagen OS: MCM log-logistic	1.2	[redacted]	[redacted]	£42,398	£35,332	1.7	[redacted]	[redacted]	£45,636	£26,845
ASA2f - Tisagen OS: MCM gen. gamma	1.2	[redacted]	[redacted]	£66,931	£55,776	1.7	[redacted]	[redacted]	£55,768	£32,805
ASA3a - Tisagen EFS: MCM exponential	1.2	[redacted]	[redacted]	£42,467	£35,390	1.7	[redacted]	[redacted]	£45,672	£26,866
ASA3b - Tisagen EFS: MCM Weibull	1.2	[redacted]	[redacted]	£42,409	£35,341	1.7	[redacted]	[redacted]	£45,642	£26,848
ASA3c - Tisagen EFS: MCM Gompertz	1.2	[redacted]	[redacted]	£42,398	£35,332	1.7	[redacted]	[redacted]	£45,636	£26,845
ASA3d - Tisagen EFS: MCM log-normal	1.2	[redacted]	[redacted]	£42,271	£35,226	1.7	[redacted]	[redacted]	£45,570	£26,806
ASA3e - Tisagen EFS: MCM log-logistic	1.2	[redacted]	[redacted]	£42,344	£35,286	1.7	[redacted]	[redacted]	£45,608	£26,828
ASA3f - Tisagen EFS: MCM gen. gamma	1.2	[redacted]	[redacted]	£42,384	£35,320	1.7	[redacted]	[redacted]	£45,629	£26,841
ASA4 - Inclusion of MAIC-adjusted OS	1.2	[redacted]	[redacted]	£42,398	£35,332	1.7	[redacted]	[redacted]	£45,636	£26,845
ASA5a - Low excess mortality, SMR=1.5	1.2	[redacted]	[redacted]	£40,845	£34,037	1.7	[redacted]	[redacted]	£43,804	£25,767
ASA5b - High excess mortality, SMR=9.05	1.7	[redacted]	[redacted]	£44,495	£26,174	1.7	[redacted]	[redacted]	£48,122	£28,307
ASA6 - ELIANA utility values	1.7	[redacted]	[redacted]	£46,720	£27,482	1.7	[redacted]	[redacted]	£50,644	£29,791
ASA7 - Allo-SCT decrement from Felder-Puig *et al.*	1.2	[redacted]	[redacted]	£44,694	£37,245	1.7	[redacted]	[redacted]	£45,897	£26,998
ASA8 - Non-infused 10% comparator QALYs and costs	1.2	[redacted]	[redacted]	£46,758	£38,965	1.7	[redacted]	[redacted]	£47,931	£28,194
ASA9 - Allo-SCT cost reduced by 25%	1.2	[redacted]	[redacted]	£48,283	£40,236	1.7	[redacted]	[redacted]	£46,287	£27,228
ASA10a - IVIg given to 47% of patients for 18 months	1.2	[redacted]	[redacted]	£42,872	£35,727	1.7	[redacted]	[redacted]	£45,872	£26,983
ASA10b - Duration of IVIg treatment doubled	1.2	[redacted]	[redacted]	£47,552	£39,627	1.7	[redacted]	[redacted]	£48,194	£28,349
ASA10c - Duration of IVIg treatment=mean EFS	1.2	[redacted]	[redacted]	£79,612	£66,344	1.7	[redacted]	[redacted]	£64,103	£37,708
ASA11 - Lymphodepleting cost in non-infused = £0	1.2	[redacted]	[redacted]	£42,000	£35,000	1.7	[redacted]	[redacted]	£45,439	£26,729
ASA12 - Discount rates = 1.5%	1.2	[redacted]	[redacted]	£30,106	£25,088	1.7	[redacted]	[redacted]	£32,134	£18,902

ASA - additional sensitivity analysis; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; DM - decision modifier; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival; EFS - event-free survival; MCM - mixture-cure model; SMR - standardised mortality ratio; allo-SCT - allogeneic stem cell transplantation; IVIg - intravenous immunoglobulin

2 BACKGROUND

2.1 Disease background

Acute lymphoblastic leukaemia (ALL) is a rare type of haematological cancer which affects the blood and bone marrow. It is characterised by the overproduction of immature white blood cells which are known as lymphoblasts.[1] The proliferation of lymphoblasts in patients with ALL inhibits normal blood cell production and function and can lead to the spread and infiltration of lymphoblasts to other organs in the body, including the lymph nodes, liver, spleen, central nervous system (CNS) and testicles.[2] Symptoms of ALL commonly include "B symptoms" (including fever, weight loss and night sweats), easy bleeding or bruising, fatigue, dyspnoea and infection.[3] The involvement of extramedullary sites is common and can cause lymphadenopathy (swollen lymph nodes), splenomegaly (enlargement of the spleen) or hepatomegaly (enlargement of the liver) in around 20% of patients.

ALL can be classified into 3 groups based on immunophenotyping: precursor-B-cell ALL, mature B-cell ALL and T-cell ALL.[4] B-cell ALL is substantially more common than T-cell ALL, representing around 80% of cases in children.[5] Precursor-B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression. In around 3-5% of ALL cases in children and 25% of ALL cases in adults, patients have a specific chromosomal abnormality known as the 'Philadelphia chromosome.'

ALL is an aggressive disease which can progress rapidly and if left untreated it can lead to death within weeks or months. The incidence of ALL is strongly related to age, with over 60% of cases occurring in children and young adults under the age of 25 years.[6] The peak incidence rate for ALL is in children under the under the age of 5 years. Based on data reported by Cancer Research UK, there were 668 new cases of ALL per year in England during the period 2016-2018 and 214 deaths from ALL per year during the period 2017-2019.[6, 7] Whilst rare overall, ALL is the most common form of childhood leukaemia and accounts for approximately 25% of all childhood cancers. Data from the Haematological Malignancy Research Network (HMRN) indicate that survival for B-cell ALL is also strongly related to age, with 5-year survival estimates amongst patients aged <15 years, 15-39 years and ≥40 years of 91%, 57% and 28%, respectively.[8]

The population under consideration within this appraisal relates to patients with relapsed or refractory (R/R) B-cell ALL. Refractory ALL relates to patients who have residual leukaemia cells in their bone marrow despite receiving intensive treatment. Relapsed ALL relates to patients who have previously responded to treatment, but who have decreased numbers of normal blood cells and a return of leukaemia cells in their bone marrow. In the first-line setting, the aim of treatment for paediatric and adult ALL is to achieve complete remission (CR). The company's submission[9] (CS) states that around 80-85% of patients achieve CR following first-line chemotherapy;[10, 11] clinical advisors to the External

Assessment Group (EAG) stated that this proportion is much higher in children, and that CR rates gradually drop with increasing age. The CS states that around 15-20% of patients will subsequently suffer disease relapse. Following first relapse, the aim of treatment is to achieve CR and if eligible, to enable patients to undergo allogeneic stem cell transplantation (allo-SCT). The proportion of patients who achieve second remission remains high at around 71-93%,[12] although more than a third of patients will suffer a second relapse.[13] The chance of achieving further remission decreases with each additional relapse.

The CS[9] highlights that R/R B-cell ALL is associated with a severe burden of disease for patients and their caregivers. The CS refers to estimates of median OS reported in the R/R setting ranging from less than 3 months to 7.5 months,[14, 15] although the EAG notes that higher estimates have been reported elsewhere,[16] and that mean OS will be higher than median OS due to some patients surviving in the longer term following allo-SCT. The CS also states that R/R ALL survivors are more likely to report poor general health, functional impairment and activity limitations compared with non-relapsed survivors.[17] Because ALL affects children and young adults, some of whom are very young, the disease can have a substantial negative impact on parents, caregivers and other individuals within their support networks. The CS highlights that parents and caregivers of children with ALL may experience psychological distress, depression, anxiety, stress, emotional pressures and negative financial impacts.[18]

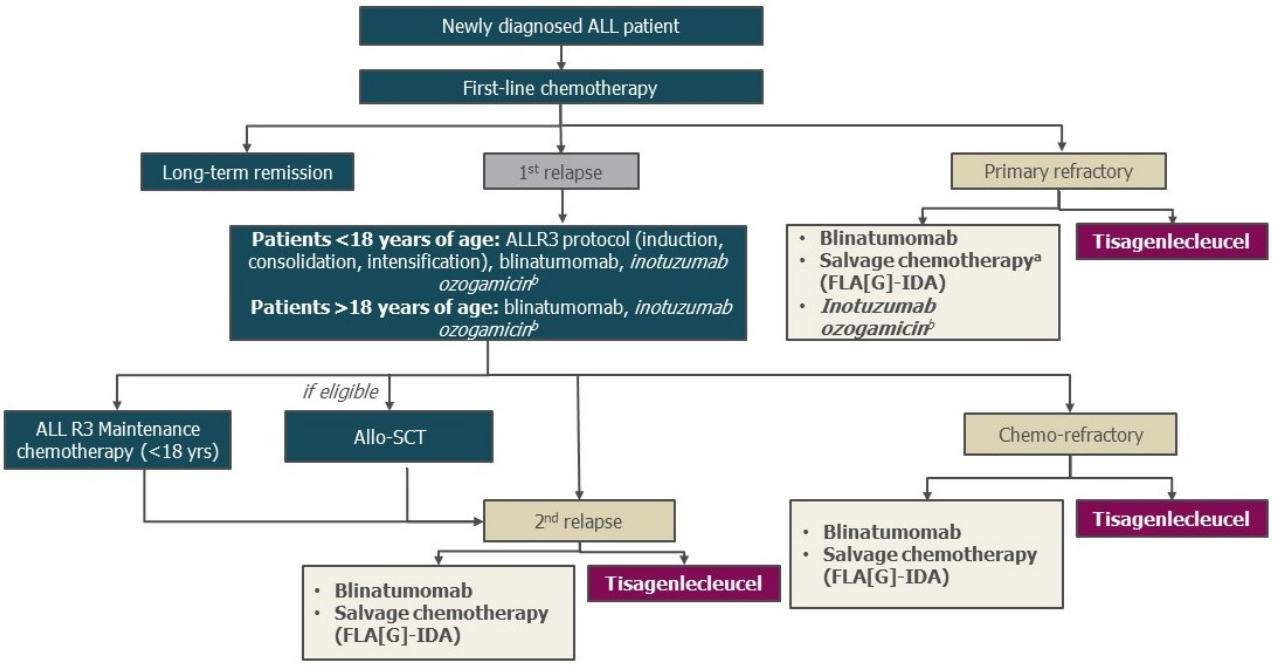
2.2 Company's overview of current service provision

2.2.1 Current treatment pathway for relapsed or refractory B-cell ALL

The company's view of the current treatment pathway for paediatric and young adult patients up to 25 years of age with B-cell ALL, together with the proposed routine positioning of tisagenlecleucel, is reproduced in Figure 1. Current recommendations for treating R/R B-cell ALL from the National Institute for Health and Care Excellence (NICE) are summarised in Table 4.

.

Figure 1: The company's view of the treatment pathway for paediatric and young adult patients with B-cell ALL and proposed positioning of tisagenlecleucel (reproduced from CS, Figure 5)



ALL - acute lymphoblastic leukaemia; allo-SCT - allogeneic stem cell transplantation; FLA[G]-IDA - fludarabine, cytarabine, G-CSF and idarubicin; G-CSF - granulocyte-colony stimulating factor; NOPHO - Nordic Society of Paediatric Haematology and Oncology; Ph-ve - Philadelphia chromosome-negative.
[a]Guidelines note that paediatric (<16 years) may be treated according to the Nordic Society of Pediatric Haematology and Oncology (NOPHO) protocol. Patients usually receive the FLAG-IDA, as per latest UK clinician feedback.
[b]Inotuzumab ozogamicin is not licensed for use in the paediatric population.

Table 4: Current NICE recommendations for treatments for R/R B-cell ALL

NICE TA	NICE recommendation
TA554 - Tisagenlecleucel (2018)[19]	Tisagenlecleucel therapy is recommended for use within the CDF as an option for treating R/R B-cell ALL in people aged up to 25 years, only if the conditions in the managed access agreement are followed.
TA541 - Inotuzumab ozogamicin (2018)[20]	Inotuzumab ozogamicin is recommended, within its marketing authorisation, as an option for treating R/R CD22-positive B-cell precursor ALL in adults. People with R/R Philadelphia-chromosome-positive disease should have had at least 1 tyrosine kinase inhibitor. Inotuzumab ozogamicin is recommended only if the company provides it according to the commercial arrangement
TA450 - Blinatumomab (2017)[21]	Blinatumomab is recommended within its marketing authorisation as an option for treating Philadelphia-chromosome-negative R/R precursor B-cell ALL in adults, only if the company provides it with the discount agreed in the PAS. Note: In 2018, the European marketing authorisation for blinatumomab was expanded to include paediatric patients aged 1 year or older.
TA893 - Brexucabtagene autoleucel (2023)[22]	Brexucabtagene autoleucel is recommended for use within the CDF as an option for treating R/R B-cell ALL in people 26 years and over. It is recommended only if the conditions in the managed access agreement for brexucabtagene autoleucel are followed.

TA - technology appraisal; R/R - relapsed/refractory; ALL - acute lymphoblastic leukaemia; CDF- Cancer Drugs Fund; PAS - Patient Access Scheme

In the UK, national guidelines for treating paediatric and young adult patients with R/R B-cell ALL are limited and patients are typically entered into experimental clinical trials.[23] With the exception of NICE Technology Appraisal (TA) 554 (tisagenlecleucel),[19] current NICE recommendations for R/R B-cell ALL[20-22] are limited to therapies which are licensed only for the treatment of adult patients. Outside of a clinical trial setting, treatment for patients with Philadelphia chromosome negative (Ph-ve) primary refractory ALL who are aged between 1 to 25 years is guided by the Children's Cancer and Leukaemia Group (CCLG) UKALL 2019 interim guidelines[24, 25] and clinicians' judgement. For patients aged under 1 year, the CCLG UKALL 2019 guidelines[24] recommend that these patients are treated according to the relevant infant ALL protocol. However, treatment recommendations for B-cell ALL at first relapse and subsequent treatment lines are not included in these guidelines.

The company's view of the overall treatment pathway for ALL, including newly diagnosed, relapsed, and refractory patients, is shown in Figure 1. For newly diagnosed ALL, recommended first-line treatment is multi-drug chemotherapy.[24] After being treated with first-line chemotherapy, if the patient experiences first relapse, preferred treatment options include blinatumomab and inotuzumab ozogamicin for adult patients which are also recommended by NICE.[20, 21] According to the CS,[9] patients who are aged under 18 years and who experience first relapse may be treated with either the ALLR3 protocol[26] or blinatumomab. Subsequently, some patients will receive maintenance chemotherapy and some eligible patients will be bridged to allo-SCT which may offer a chance of long-term cure. For patients who experience relapse following allo-SCT or who experience second or later relapse, tisagenlecleucel, which has been available through the Cancer Drugs Fund (CDF) since 2018, has become an established treatment option.[19] In the absence of tisagenlecleucel, blinatumomab and salvage chemotherapy may be considered as alternative treatment options.

For patients with primary refractory disease, existing guidelines[24] suggest that blinatumomab is typically used with the aim of bridging to allo-SCT in eligible patients. Inotuzumab ozogamicin is also licensed for the treatment of adults with the aim of either bridging to allo-SCT or subsequent tisagenlecleucel treatment. Salvage chemotherapy, either using NOPHO blocks[24] or the FLAG-IDA regimen (fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor [G-CSF]) might be options for a minority of patients when blinatumomab or inotuzumab ozogamicin are not suitable treatments.[19, 24, 27]

2.2.2 Company's proposed positioning of tisagenlecleucel

The company's proposed positioning of tisagenlecleucel in England is in line with its full licensed indication for tisagenlecleucel, that is, for paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.[28]

2.2.3 EAG clinical advisors' views

The EAG's clinical advisors broadly agreed with the company's description of the disease and the proposed positioning of tisagenlecleucel. The clinical advisors commented that two additional drugs - asparaginase and daunorubicin – should be included in the description of the first-line chemotherapy regimens. They also commented that for primary refractory patients, inotuzumab ozogamicin may be an available option, but it is usually less preferable due to the risk of veno-occlusive disease (VOD) if it is used just before allo-SCT. The clinical advisors also mentioned that whilst inotuzumab ozogamicin only has a marketing authorisation for use in adults, it is used off-label in paediatric patients with R/R ALL. The advisors highlighted that for patients at first relapse, the ALLR3 protocol is no longer the standard of care in the UK due to its high mortality rate, and that since blinatumomab has become available for treating relapse, blinatumomab followed by allo-SCT has become the preferred treatment in high-risk patients. For patients at second or later relapse, the choice of treatment depends on the CD-19 status in patients: if the patient has become CD-19 negative following treatment with blinatumomab (during the first relapse treatment), then neither tisagenlecleucel nor blinatumomab would be an option. For patients with second or later ALL relapse, the EAG's clinical advisors agreed with the treatment pathway only for patients with CD-19 positive ALL.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[9] A summary of the decision problem as outlined in the final NICE scope[29] and addressed in the CS is presented in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: The decision problem (reproduced from CS, Table 2, with minor amendments by the EAG)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	Children and young adults up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse	As per NICE final scope
Intervention	Tisagenlecleucel	Tisagenlecleucel	As per NICE final scope
Comparator(s)	Established clinical management without tisagenlecleucel-T including: • Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy • Clofarabine (off label) • Inotuzumab ozogamicin (CD22-positive B-precursor ALL) • Blinatumomab (Philadelphia-chromosome-negative ALL) • A TKI such as dasatinib, imatinib or ponatinib alone or in combination with FLAG-based combination chemotherapy (Philadelphia-chromosome-positive ALL) • SCT • Best supportive care (including palliative care)	• FLAG-IDA • Blinatumomab	• The comparators of relevance to this submission reflect treatments currently licensed and used in the population of interest in this submission: patients under the age of 25 with ALL which is refractory, in relapse post-transplant, or in second or later relapse • Inotuzumab ozogamicin does not form a relevant comparator in this appraisal as it is not licensed for use in patients under 18, and is only recommended by NICE in adult patients with ALL.[20] Additionally, clinical feedback received as part of this appraisal suggests that inotuzumab ozogamicin is commonly used earlier in the treatment pathway, following first relapse, to a lesser extent in primary refractory patients and typically as a bridge to SCT or tisagenlecleucel).[27] Tisagenlecleucel is not licensed for use at first relapse (a population not covered by the scope of this appraisal),[28] whilst primary refractory patients only form a small part of the eligible patient population for tisagenlecleucel (only 7.6% of patients in the pivotal ELIANA trial had primary refractory disease).[30] The small proportion of patients with primary refractory disease in the ELIANA trial is representative of real-world clinical practice, as mentioned by clinical expert feedback received in TA554.[19] Clinical feedback also indicated that: o tisagenlecleucel is often reserved for use following treatment failure of inotuzumab ozogamicin in primary refractory patients, [27] and o inotuzumab ozogamicin is rarely considered a suitable treatment option for patients who have experienced a relapse post allo-SCT given the high risk of veno-occlusive disease (VOD)[27]

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
			• There is therefore limited overlap in the populations eligible for treatment with inotuzumab ozogamicin and tisagenlecleucel • SCT is used as consolidation therapy following complete remission with prior treatment, such as blinatumomab or salvage chemotherapy, and does not constitute a standalone treatment option. As such, a comparison to SCT alone is not appropriate. The benefits of SCT are already implicitly captured for modelled comparator treatments: trial data informing treatment benefit include a proportion of patients who received SCT subsequent to complete remission (where eligible). The costs of subsequent SCT are explicitly captured in comparator treatment costs. Patients receiving tisagenlecleucel can also receive SCT as a subsequent treatment (22.8% of patients in the ELIANA trial received a subsequent SCT), further precluding its consideration as a standalone comparator. SCT was not specified as a relevant comparator in the original submission for tisagenlecleucel in this indication (TA554), and its exclusion as a comparator in that submission was not raised as a key issue by the committee. Given its use in clinical practice has not changed (it is still used as consolidation following remission with a prior treatment), its exclusion as a comparator remains appropriate in this appraisal • The proportion of patients with Ph+ve ALL within the eligible patient population for tisagenlecleucel constitute a small minority (<3%)[12] and therefore TKIs are not considered to represent relevant comparators to this submission, in line with TA554.[19] Furthermore, given the eligibility criteria of the tisagenlecleucel clinical trials, patients had to have tried and failed two prior lines of TKI therapy, and previous feedback from UK clinical experts is that the use of a 3rd TKI does not constitute standard practice[27] • Clinical feedback received as part of both the original submission (TA554) and this submission indicated that FLAG-IDA is the predominant chemotherapy regimen in patients with relapsed disease,[27, 31] being associated with similar remission rates to clofarabine, with lower toxicity. As such, clofarabine does not represent standard NHS practice in this indication, and is not considered a relevant comparator

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival (including relapse-free and event-free survival) • Response rate (including MRD and haematologic responses and complete remission) • Rate of allogeneic stem cell transplant (allo-SCT) • Adverse effects of treatment • Health-related quality of life.	• Overall survival • Event-free survival • Relapse-free survival • Response rate (including MRD, haematological responses and complete remission) • Rate of allo-SCT • Adverse effects of treatment • Health-related quality of life (EQ-5D-3L and PedsQL)	In line with the final NICE scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY) • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	The economic analysis will align with reference case stipulations as noted in the scope, however, non-reference case discounting of 1.5% will also be considered.	As noted in the case for change consultation document for the NICE methods of health technology evaluation, *"NICE understands there is broad interest in potentially curative technologies including advanced therapy medicinal products (ATMP), and a policy-level drive to support them"*.[32] The report explored the use of a non-reference case discount of 1.5% for these technologies that have high upfront costs and long-term health benefits such as ATMPs and other one-off treatments. Furthermore, Section 4.5.3 of the NICE health technology evaluations manual (2022), [33] states that the "committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects if, in the committee's considerations, all of the following criteria are met: • The technology is for people who would otherwise die or have a very severely impaired life • It is likely to restore them to full or near-full health • The benefits are likely to be sustained over a very long period" Given tisagenlecleucel is an ATMP with curative potential, thus generating a large number of incremental QALYs (see CS, Section B.3.9), and is a one-off treatment cost, consideration of a non-reference case discount of 1.5% is justified.

3.1 Population

The target population for tisagenlecleucel defined in the CS[9] relates to children and young adults up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. This is consistent with the NICE scope[29] and the marketing authorisation for tisagenlecleucel[28] (see Section 3.2). The three clinical studies of tisagenlecleucel which are reported in Section B.2 of the CS (ELIANA,[34] ENSIGN[35] and B2102J[36]) are consistent with this population. The EAG notes that ELIANA and ENSIGN, each applied a minimum age eligibility criterion of 3 years, whereas B2101J included patients aged 1-24 years. The Summary of Product Characteristics (SmPC) for tisagenlecleucel[28] highlights that there is limited experience with this treatment in paediatric patients below the age of 3 years.

The EAG's clinical advisors commented that the patients who received the infusion in the tisagenlecleucel studies were representative of the patients receiving this treatment in the NHS. The EAG notes that the age distribution of patients who have received tisagenlecleucel through the CDF[37] is generally similar to the distributions in the tisagenlecleucel studies.[34-36]

3.2 Intervention

The intervention described in the CS[9] is consistent with the final NICE scope.[29] The intervention under consideration is tisagenlecleucel (Kymriah®). Tisagenlecleucel is licensed for the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.[28] Tisagenlecleucel also holds a marketing authorisation for use in adult patients with R/R diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, and for adult patients with R/R follicular lymphoma (FL) after two or more lines of systemic therapy. The SmPC for tisagenlecleucel describes the technology as *"a genetically modified autologous cell-based product containing T cells transduced ex vivo using a lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked via a human CD8 hinge and transmembrane region to an intracellular signalling chain of human 4-1BB (CD137) co-stimulatory domain and CD3-zeta signalling domain."*[28]

A full European Union (EU) marketing authorisation for tisagenlecleucel was issued for the treatment of paediatric and young adult patients with R/R B-cell ALL in August 2018.[28] Tisagenlecleucel is administered by intravenous (IV) infusion with an intended target dose of 0.2 to 5.0×10^6 tisagenlecleucel cells per Kg body weight for patients with a body mass of ≤50 Kg, or 0.1 to 2.5×10^8 tisagenlecleucel cells (non-weight based) for patients with a body mass of >50 Kg. The intervention requires three phases of pre-treatment before infusion of tisagenlecleucel, which are comprised of (in order): (a) leukapheresis and cryopreservation – which is used to obtain T-cells from the patient; (b)

bridging chemotherapy - which is used to stabilise the disease and (c) lymphodepleting chemotherapy which establishes an immune environment conducive to product expansion and persistence prior to the tisagenlecleucel infusion. After completion of lymphodepleting chemotherapy, tisagenlecleucel is administered via a single IV infusion. The SmPC states that tisagenlecleucel must be administered in a qualified treatment centre and that therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with tisagenlecleucel. According to the company, the current manufacturing time of tisagenlecleucel in the UK is 3 weeks.[9, 38] The time from enrolment to infusion in the tisagenlecleucel studies was longer, with mean estimates within each study ranging from 42.4 to 67.5 days.[38]

The list price for tisagenlecleucel is £282,000.00 as a one-off cost. The company has an agreed Patient Access Scheme (PAS) discount of [redacted]. The price of tisagenlecleucel including this PAS discount is [redacted] The company has confirmed that payment for tisagenlecleucel is only made for patients who are successfully infused; in instances in which a patient is not successfully infused with tisagenlecleucel, either due to manufacturer error, patient disease progression or death, the company will bear the cost (see clarification response,[38] question C8). Invoices are issued to the treatment centre when they accept receipt of tisagenlecleucel into the treatment centre. According to the company, between the 16th November 2018 and the 30th June 2023, there were 160 unique patient applications to NHS England (NHSE) for tisagenlecleucel; of these, there were 136 successful tisagenlecleucel infusions (85%).

The administration of CAR-T therapies is covered under an NHSE tariff.[22] Based on information provided by NICE, the EAG understands that this tariff includes the following costs components: leukapheresis; administration of the CAR-T in hospital; short-term adverse events (AEs) in hospital, monitoring up to 100 days and training. The tariff does not include acquisition costs of the bridging chemotherapy, lymphodepleting chemotherapy, the CAR-T product, subsequent stem cell transplantation (SCT) or other subsequent treatments.

3.3 Comparators

The NICE scope[29] defines the comparator as *"established clinical management without tisagenlecleucel-T"*, and lists several comparator therapies, including salvage chemotherapies (FLAG-IDA and clofarabine), monoclonal antibodies (inotuzumab ozogamicin and blinatumomab), tyrosine kinase inhibitors (TKIs; such as dasatinib, imatinib or ponatinib alone or in combination), SCT and BSC. The tisagenlecleucel studies (ELIANA,[34] ENSIGN[35] and B2101J[36]) are all single-arm studies. The CS[9] presents indirect comparisons of tisagenlecleucel versus blinatumomab and against salvage chemotherapy. The company's economic model compares tisagenlecleucel against blinatumomab and

FLAG-IDA (using data from a study of clofarabine as a proxy). The CS gives the following justifications for the exclusion of the other comparator therapies listed in the NICE scope:

- *Inotuzumab ozogamicin:* The CS highlights that this treatment is only licensed and recommended by NICE for people aged over 18 years of age. The company also states that this treatment is typically used earlier in the treatment pathway.
- *TKIs:* The CS states that TKIs are not relevant comparators because only a minority of the target population have Philadelphia-positive (Ph+ve) ALL. The CS also notes that patients with Ph+ve disease who were enrolled in the tisagenlecleucel studies had to have failed two prior lines of TKI therapy, and the use of TKIs at third-line does not constitute standard practice.
- *SCT:* The CS argues that SCT is a consolidation treatment rather than a standalone treatment option. The CS notes that SCT forms part of the pathway for patients receiving tisagenlecleucel, blinatumomab or FLAG-IDA in the economic model.
- *BSC:* The CS does not provide a justification for the exclusion of BSC as a comparator.

The EAG notes the following points regarding the relevant comparators for tisagenlecleucel:

- Blinatumomab is licensed in both adults and children, but the wording of the NICE recommendation in TA450 is limited to adults only. The EAG understands that blinatumomab is used in the treatment of paediatric R/R ALL in NHS practice.
- Inotuzumab ozogamicin is only licensed as a treatment for adult patients. However, the EAG's clinical advisors commented that this treatment is used off-label in paediatric patients with ALL. The EAG's clinical advisors commented that this treatment would typically not be used in patients prior to allo-SCT due to the risk of VOD.
- Whilst the company has focussed on the use of FLAG-IDA as the salvage chemotherapy regimen of choice, the EAG's clinical advisors commented that NOPHO blocks may be used instead.
- The EAG's clinical advisors commented that blinatumomab is likely to reflect the main comparator for tisagenlecleucel, with salvage chemotherapy only being used in instances where blinatumomab is not suitable (e.g., in patients with CD19 negative second relapse). However, the clinical advisors noted that in the future more patients will have had blinatumomab at first relapse, which may lead to uncertainty around whether this treatment can be used again to treat subsequent relapse.
- The EAG's clinical advisors stated that in the absence of tisagenlecleucel, the only treatment which offers a potential for cure is allo-SCT. The aim of blinatumomab and salvage chemotherapy in the R/R setting is to achieve CR and to enable patients to undergo transplant. Tisagenlecleucel is intended to be a curative therapy without the need for subsequent allo-SCT.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[29]

- Overall survival (OS)
- Progression-free survival (PFS), including relapse-free survival (RFS) and event-free survival (EFS)
- Response rate (including minimal residual disease (MRD) and haematologic responses and complete remission (CR))
- Rate of allo-SCT
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS[9] reports on these clinical outcomes for all three tisagenlecleucel studies (ELIANA, ENSIGN and B2101J),[34-36] except for rates of allo-SCT which were reported only for ELIANA. Allo-SCT rates for ENSIGN and B2101J were provided separately in the company's clarification response.[38] AE data are reported for all three tisagenlecleucel studies. HRQoL data from one of the tisagenlecleucel studies (ELIANA) are reported in the clinical and economic sections of the CS, albeit only for patients aged 8 years or older. For the comparators, only OS, allo-SCT rates and AE frequencies are reported. The company's base case economic model uses data from the tisagenlecleucel studies on EFS, OS, rates of allo-SCT, and AEs. Euroqol 5-Dimensions (EQ-5D) data from ELIANA are included in the company's scenario analyses. Further details on the company's model can be found in Section 5.

3.5 Other relevant factors

The CS[9] states that there are no anticipated issues relating to equality. The CS highlights that people with R/R ALL who are aged 26 years or older already have access to CAR-T therapy (brexucabtagene autoleucel; NICE TA893[22]) via the CDF and notes that routine commissioning of tisagenlecleucel would ensure that people with ALL aged under 26 years have access to a CAR-T therapy, regardless of their age.

The EAG notes that the company has made a case that tisagenlecleucel is an advanced therapy medicinal product (ATMP) with curative potential. As such, the CS[9] includes economic analyses which adopt non-reference case discount rates of 1.5% for health outcomes and costs. The results of these analyses are presented in Section 5.2.6. Non-reference case discount rates are also considered in the EAG's sensitivity analyses (see Section 5.6).

4 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[9] is comprised of:

- A systematic literature review (SLR)
- Summary and results for the studies of tisagenlecleucel
- Indirect treatment comparisons (ITCs) of tisagenlecleucel vs. blinatumomab or salvage chemotherapy.

This chapter summarises and critiques the company's review methods, clinical effectiveness data and ITCs. Full details are presented in the CS[9] Section B.2 and CS Appendix D.[39]

4.1 Critique of the methods of review

4.1.1 Searches

CS Appendix D[39] reports an SLR to identify any published evidence on the clinical efficacy/effectiveness and safety of treatments used in the population as described in the decision problem. Somewhat confusingly, there were three iterations of the SLR (in 2018, 2019 and March 2023); while described as "updates" these used substantively different search approaches, platforms and limits each time (as reported in exhaustive detail in Appendix D.1.1). However, rather than provide three separate critiques, the EAG has instead attempted to evaluate the cumulative effectiveness of the overall search approach across all three phases.

Generally, the later search iterations appear to overcome most of the issues with the earlier ones; for example, an age limit used in the 2018 version was superseded by later updates without such a limit, meaning there was no overall impact on retrieval. The only persistent limit that applied in 2019 was that restricting the searches to English and German language material only; since, even though the same limit was not applied in 2023, the new search was only backdated as far as 2019. However, the EAG is broadly satisfied with the company's clarification response[38] (question A1) that any impact on the number of results would be marginal given that only English language studies were eligible for inclusion, and that they therefore judged it unnecessary to re-run the searches for the earlier period.

Overall, the searches appear to have been designed and executed with competence. Controlled vocabulary (e.g., MeSH) is used alongside free text search terms for the population and interventions of interest. All the key database sources required by NICE have been covered (MEDLINE including Medline-in-Process and Epub ahead of print, Embase and Cochrane Library plus the Database of Abstracts of Reviews of Effects [DARE] via the Centre for Reviews and Dissemination [CRD] website). Searches also included relevant trials registers (only the WHO International Clinical Trials Registry Platform for the March 2023 searches, although earlier iterations had included additional sources). In April 2023, conference proceedings including the American Society of Clinical Oncology (ASCO) and

the European Society of Medical Oncology (ESMO) were searched from January 2021 to December 2022. The EAG considers it unlikely that any relevant studies have been missed as a consequence of the search approach.

4.1.2 Inclusion criteria for the SLR

The company's SLR aimed to identify studies of tisagenlecleucel and other interventions for children and young adults up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. Interventions included tisagenlecleucel and any approved or guideline-recommended therapies. Includable studies had to report relevant effectiveness or safety outcomes. Includable study designs were randomised controlled trials (RCTs; with at least 10 patients per arm), single-arm clinical studies (including at least 20 patients) and prospective and retrospective observational studies (including at least 20 patients). Inclusion was limited to studies published since the year 2000 in the English language. Full eligibility criteria are described in Tables 13 and 14 of CS Appendix D.1.1.[39]

The EAG believes the inclusion criteria to be appropriate to identify relevant studies of tisagenlecleucel and comparator treatments. However, the EAG considers there are major issues with the transparency of study selection for the comparator studies for the ITCs. This is discussed further in Section 4.8.

4.1.3 Critique of study selection, data extraction and quality assessment

Two reviewers screened all citations and full-text articles (CS Appendix D.1.2[39]). Extracted data were checked by a second reviewer. Study quality for non-randomised interventional studies was assessed using the Good Research for Comparative Effectiveness (GRACE) checklist[40] for studies identified via the 2018 and 2019 searches. The CS (Appendix D.1.2[39]) states that, for the 2023 SLR update, non-randomised studies were assessed via the Risk Of Bias In Non-randomised Studies - Interventions (ROBINS-I) tool[41] and RCTs were assessed via the CRD checklist;[42] however, no assessments using the ROBINS-I or CRD checklists are presented, and all critical appraisals in the CS use the GRACE checklist.[40] Overall, the EAG considers these methods to be appropriate.

4.1.4 Overall EAG view on company's review methods

Overall, the EAG considers that the company's review methods were generally appropriate. However, the EAG believes there are major issues with the transparency of study selection for the comparator studies for the ITC. This is discussed further in Section 4.8.

4.2 Characteristics of studies of tisagenlecleucel

4.2.1 Results of the company's SLR

The company's clinical SLR identified three single-arm clinical studies of tisagenlecleucel in R/R B-cell ALL in children and young adults (reported within 10 publications): ELIANA,[34] ENSIGN[35] and

B2101J.[36] Further detail of the SLR results is provided in Section B.2.1 of the CS,[9] and CS Appendix D.[39] The company's SLR also identified studies of comparator treatments relevant to the ITC, which are described in Section 4.8 of this EAG report. In addition, the CS (Section B.2 overview) cites the NHSE CDF report[37] which captures Systematic Anti-Cancer Therapy (SACT) data from patients receiving tisagenlecleucel in England during the managed access period. These data are described in Section 4.2.3.

4.2.2 Study design and setting for tisagenlecleucel studies

An overview of the three tisagenlecleucel clinical studies ELIANA,[34] ENSIGN[35] and B2101J[36] is provided in Table 6 (further detail is provided in CS,[9] Section B.2.2 and B.2.3). All three studies were single-arm. ELIANA and ENSIGN were multicentre studies with similar designs (ELIANA was international while ENSIGN was US-based), whereas B2101J was an earlier US-based single-centre study to determine the safety, tolerability and engraftment potential of tisagenlecleucel. In ELIANA, of all infused patients, 39 were in the US, 6 in Canada, 6 in Japan, 1 in Australia, and 28 in Europe; none were based in the UK (see clarification response,[38] question B6).

Population and setting in tisagenlecleucel studies

All three studies[34-36] included patients with R/R B-cell ALL which was either primary refractory, chemo-refractory, relapsed post-SCT, in second or later relapse, or ineligible for SCT (chemo-refractory was defined as not achieving CR after 1 cycle of chemotherapy for relapsed disease). Lymphoma patients were also eligible for ENSIGN and B2101J but are not included in the data in the CS[9] for this appraisal. ELIANA and ENSIGN included patients aged 3 years at screening to 21 years at initial diagnosis (the final populations included patients up to age 24 or 25 years at study entry), while B2101J included patients aged 1-24 years. The study populations broadly matched the population defined in the final NICE scope.[29] The EAG's clinical advisors stated that the study populations generally reflected patients who would be eligible for treatment in England.

Table 6: Design of the three tisagenlecleucel studies (adapted from CS, Tables 4 and 5)

Study	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Key references (not final data cut)	Laetsch *et al.* (2022)[30]	Maude *et al.* (2016)[43]	Maude *et al.* (2014)[44]
Study design	• International, multicentre • Phase II, single-arm, open-label study • To assess efficacy, safety and patient-reported outcomes	• US-based, multicentre • Phase II, single-arm, open-label study • To assess efficacy and safety	• US-based, single centre • Phase I/IIa, single-arm, open-label study • To assess the safety, tolerability and engraftment potential of tisagenlecleucel
Location	• 25 centres across the US, EU (Austria, Belgium, France, Germany, Italy, Spain), Norway, Canada, Australia, and Japan	• 13 centres across the US	• Children's Hospital of Pennsylvania in the US
Population	• Paediatric and young adult patients • Aged 3 years at screening to 21 years at initial diagnosis • R/R B-cell ALL (primary refractory, chemo-refractory, relapsed post-SCT, in second or later relapse, or ineligible for SCT) • N=97 (enrolled); N=79 (infused)	• Paediatric and young adult patients • Aged 3 years at the time of screening to 21 years at initial diagnosis • R/R B-cell ALL (primary refractory, chemo-refractory, relapsed post-SCT, in second or later relapse, or ineligible for SCT) • Also B-cell lymphoblastic lymphoma but not included in CS[a] • N=75 (enrolled); N=64 (infused)	• Paediatric and young adult patients • Aged 1–24 years • R/R B-cell ALL (treatment refractory, relapsed post-SCT, or ineligible for SCT) • Also lymphoma but not included in CS[a] • N=67 (enrolled); N=57 (infused); Ns for non-CNS3 ALL cohort[b]
Intervention(s)	Single dose of tisagenlecleucel administered as an IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg body weight (for patients ≤50 kg) • 0.1 to 2.5×10^8 tisagenlecleucel cells (non-weight based) (for patients >50 kg)[c]	Single dose of tisagenlecleucel administered as a single IV infusion with a target dose range of: • 0.2 to 5.0×10^6 tisagenlecleucel cells per kg (for patients ≤50 kg) • 0.1 to 2.5×10^8 tisagenlecleucel cells (for patients >50 kg)[c]	Tisagenlecleucel administered as an IV infusion with intra-patient dose escalation over one, two or three infusions: • Maximum total dose of 1.5×10^7 to 5×10^9 (0.3×10^6 to 1.0×10^8/kg) total cells (starting with a 10% fraction dose reduction but allowing for intra-patient dose escalation)
Comparator(s)	N/a – single-arm study	N/a – single-arm study	N/a – single-arm study
Used in marketing authorisation	Yes	Yes	Yes
Used in model	Yes	No	No

Study	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Reported outcomes in decision problem	ORR, ORR with MRD-negative bone marrow, **EFS,** DoR, RFS, **OS,** Patient-reported outcomes (EQ-5D-3L), Safety	ORR, ORR with MRD-negative bone marrow, EFS, DoR, RFS, OS, Safety	ORR, ORR with MRD-negative bone marrow, EFS, DoR, OS, Safety
Duration of study and follow-up	• Study initiated on 8th April 2015 and completed on 17th November 2022 • Primary and secondary follow-up: 5 years following infusion (or until premature withdrawal). Patients continue to be followed until 15 years post-infusion	• Study initiated on the 14th August 2014 and completed on 24th May 2019 • Primary and secondary follow-up: 5 years following infusion (or until premature withdrawal). Patients continue to be followed until 15 years post-infusion	• Study was initiated on 15th March 2012 and completed on 7th May 2018 • Primary and secondary follow-up: 2 years following infusion. Patients continue to be followed until 15 years post-infusion
Final DCO; median follow-up	• DCO 17th November 2022 • Median follow-up 79.4 months (6.6 years)	• DCO 24th May 2019 • Median follow-up 31.7 months (2.6 years)	• DCO 7th May 2018 • Median follow-up 47.2 months (3.9 years)

Outcomes highlighted in bold are included in the economic model

[a]*In latest data cuts for ENSIGN and B2101J, one patient with lymphoma had been infused in B2101J. Populations treated and analysed within submission restricted to patients with R/R B-cell ALL.*

[b]*Data for the non-CNS3 cohort only are presented within submission.*

[c]*A target per-protocol dose of tisagenlecleucel transduced cells for paediatric patients consists of a single infusion of 2.0 to 5.0×10^6 transduced cells per kg body weight (for patients ≤50 kg) and 1.0 to 2.5×10^8 tisagenlecleucel transduced viable T-cells (for patients >50 kg). The following cell dose ranges here were infused if all other safety release criteria were met.*

ALL - acute lymphoblastic leukaemia; CD19 - cluster of differentiation 19; CNS - central nervous system; DCO - data cut-off; DoR - duration of remission; EFS - event-free survival, EQ-5D-3L - Euroqol 5-Dimensions 3-Levels; IV - intravenous; MRD - minimal residual disease; N/a - not applicable; ORR - overall remission rate; OS - overall survival; RFS - relapse-free survival; R/R - relapsed/refractory; US 0 United States.

Sources: ELIANA CSR (17th Nov 2022); ENSIGN CSR (24th May 2019); B2101J CSR (7th May 2018); Laetsch et al. (2022).

Intervention in tisagenlecleucel studies

All three studies[34-36] followed a similar design, with sequential phases of screening, enrolment, treatment (including apheresis, bridging chemotherapy, lymphodepleting chemotherapy and tisagenlecleucel administration) and follow-up. In ELIANA and ENSIGN, patients were screened following leukapheresis and eligible patients were then enrolled, while in B2101J leukapheresis could occur prior to or after enrolment. In all three studies, patients were then treated with bridging chemotherapy (where appropriate) followed by lymphodepleting chemotherapy 2–14 days prior to tisagenlecleucel infusion. The study designs for ELIANA and B2101J are shown in Figures 6 and 7 of the CS[9] (ENSIGN was similar to ELIANA in design).

Patients in ELIANA[34] and ENSIGN[35] received a single IV infusion of tisagenlecleucel, while in B2101J[36] tisagenlecleucel infusion was administered in a dose-escalated manner (23% had one infusion, 44% had two infusions, 28% had 3 infusions, 5% had >3 infusions; see clarification response,[38] question B7). The company's clarification response states that the dose escalation approach was unlikely to have impacted on outcomes, based on the similarity of outcomes between studies. The EAG's clinical advisors agreed with this view.

Outcomes in tisagenlecleucel studies

The following outcomes specified in the decision problem were reported in all three studies:

- Overall remission rate (ORR) = complete remission (CR) or complete remission with incomplete blood count recovery (CRi)
- ORR with minimal residual disease (MRD)-negative bone marrow (MRD <0.01%)
- Event-free survival (EFS)
- Duration of remission (DoR)
- Relapse-free survival (RFS)
- Overall survival (OS)
- Safety
- Patient-reported outcomes (ELIANA only).

Definitions for time-to-event outcomes were as follows (CS,[9] Section B.2.3.2):

- EFS: Time from first tisagenlecleucel infusion to the earliest date of: death due to any cause, relapse, or treatment failure (treatment failure defined as no response and discontinuation from the study due to: death, AE, lack of efficacy, or a new anticancer therapy)
- DoR: Time from CR or CRi to relapse or death due to underlying cancer
- RFS: Time from CR or CRi to relapse or death due to any cause during CR or CRi
- OS: Time from first tisagenlecleucel infusion to death due to any reason.

Issues with EFS definition in tisagenlecleucel studies

As noted above, the EFS definition in the tisagenlecleucel studies considered an "event" to include death due to any cause, relapse, or treatment failure (treatment failure defined as no response and discontinuation from the study due to: death, AE, lack of efficacy, or a new anticancer therapy). The company's economic model uses EFS data from ELIANA[34] which includes censoring for allo-SCT and further anticancer therapy (see Section 5 of this report).

The EAG's clinical advisors raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from more stringent definitions of EFS. ELIANA-defined EFS does not consider MRD positivity as an event, and also includes censoring for allo-SCT and further therapy. The clinical advisors stated that this approach may introduce a bias which may exaggerate the absolute benefits of tisagenlecleucel on EFS, particularly if the indication for further therapy/allo-SCT was the detection of MRD positivity or loss of B-cell aplasia following tisagenlecleucel, as this may indicate that the treatment has failed but this failure would be masked by the censoring mechanism.

The clinical advisors referred to a recent national UK analysis of real-world outcomes for 128 children and young adults who received tisagenlecleucel.[45] This study reported on EFS outcomes defined in two ways: firstly using ELIANA-defined EFS (where events included death, relapse, or failure to respond by day 30, and patients were censored for further therapy), and secondly using a more stringent definition of EFS which included all clinically relevant events (including molecular or frank relapse, further therapy, death or treatment failure). This study reports median EFS by the ELIANA definition of 22 months and median EFS based on stringent criteria of 7 months, indicating a substantial impact of the differing definitions; this is discussed further in Section 4.4.

Data cut-offs and follow-up duration in tisagenlecleucel studies

The data cut-offs were as follows (also shown in Table 6).

- ELIANA: Data cut-off 17th November 2022; median follow-up 79.4 months (6.6 years)
- ENSIGN: Data cut-off 24th May 2019; median follow-up 31.7 months (2.6 years)
- B2101J: Data cut-off 7th May 2018; median follow-up 47.2 months (3.9 years)
- NHSE SACT data:[37] Data cut-off 21st July 2023; median follow-up 17.6 months (1.5 years).

The data in the CS[9] are based on the Clinical Study Reports (CSRs).[34-36] The company's clarification response[38] (question B3) confirmed that no subsequent data cuts are expected for any of the studies.

Analysis populations and participant flow in tisagenlecleucel studies

The analysis populations for the three studies are shown in Table 7. The CONSORT flow diagrams are presented below in Figure 2, Figure 3 and Figure 4 (company's clarification response,[38] question B5).

The full analysis set consisted of all patients receiving tisagenlecleucel infusion; this population was used for the effectiveness and safety results presented in the CS.[9] However, patients who were screened (i.e., had leukapheresis in ENSIGN[35] and ELIANA[34]) but who did not receive a tisagenlecleucel infusion were not included in the effectiveness and safety results. The percentage of patients who were screened and had leukapheresis but were not infused was 31% in ELIANA and 25% in ENSIGN (percentage not reported for B2101J[36]). Reasons for discontinuation prior to infusion are shown in Figure 2, Figure 3 and Figure 4.

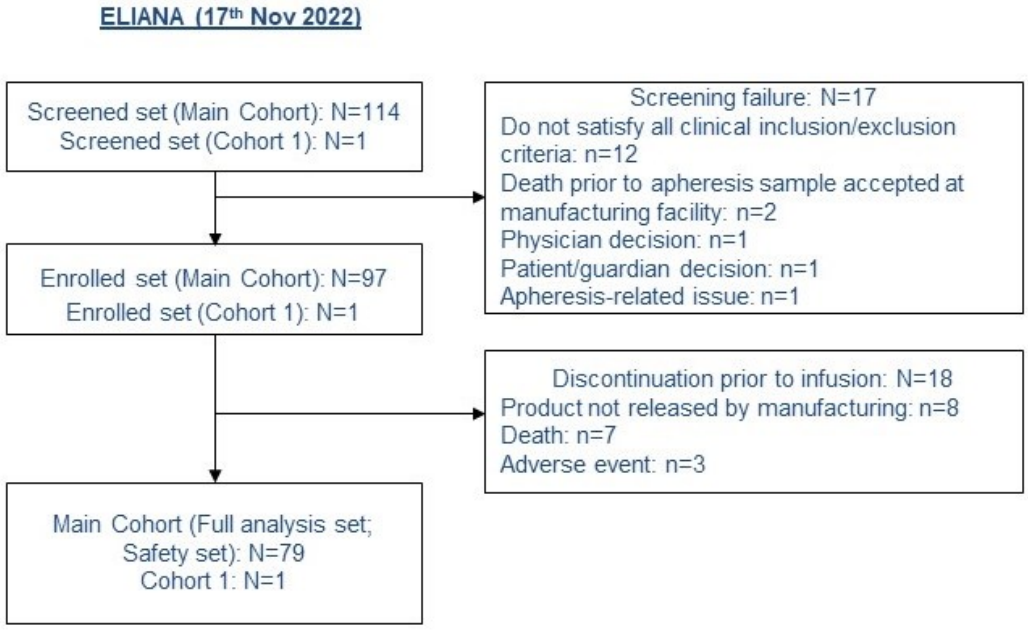
With respect to the NHSE SACT dataset,[37] the company's clarification response[38] (question B13) states that of 160 applications for unique patients, 136 (85%) successful tisagenlecleucel infusions were performed in UK clinical practice. One hundred and twenty-one of these infusions were done in England.

Table 7: Study analysis populations (adapted from CS, Tables 8 and 9)

Analysis set, n (%)	Description	ELIANA	ENSIGN	B2101J[a]
Screened set	All screened patients (patients were screened and enrolled after leukapheresis in ELIANA and ENSIGN, while in B2101J leukapheresis could occur prior to or after enrolment)	114 (100)	85 (100)	-
Enrolled set	Met inclusion criteria. For ELIANA and ENSIGN, leukapheresis product accepted by manufacturing facility	97 (85)	75 (88)	67 (100)
Screened but not infused	Screened (and had leukapheresis in ELIANA and ENSIGN) but not infused with tisagenlecleucel	35 (31)	21 (25)	-
Full analysis set	All patients receiving tisagenlecleucel infusion	79 (69)	64 (75)	57 (85)
Efficacy analysis set[b]	All patients infused ≤6 months before data cut-off	79 (69)	64 (75)	-
Safety set	All patients receiving tisagenlecleucel infusion	79 (69)	64 (75)	57 (85)

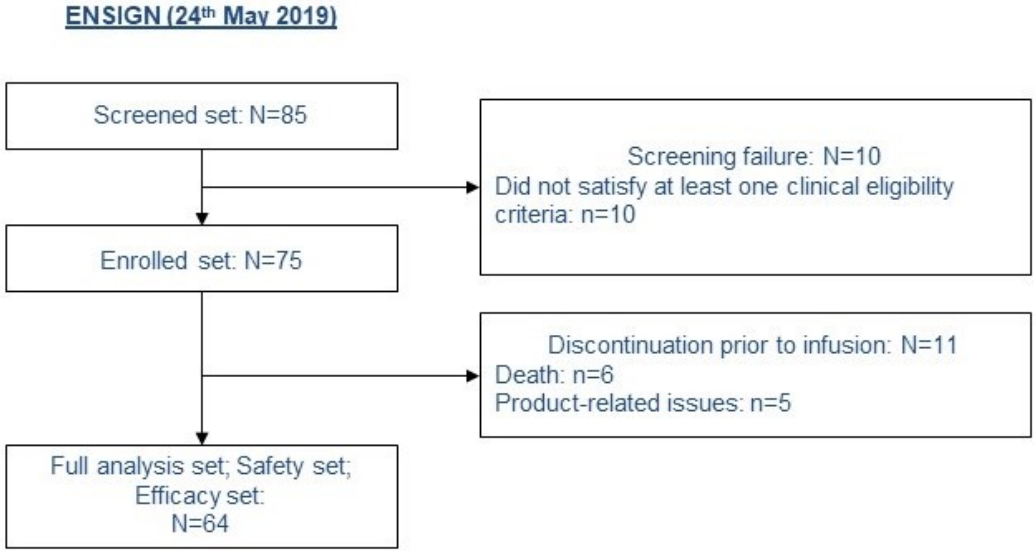
[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b]The efficacy analysis set was used only for outcomes related to ORR in ENSIGN. There was no requirement for an efficacy analysis set in B2101J, hence the FAS was used for all outcomes.
ALL - acute lymphoblastic leukaemia; CNS - central nervous system; FAS - full analysis set ; ORR - overall remission rate.
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018).

Figure 2: CONSORT diagram of patient flow for ELIANA (reproduced from company's clarification response, Figure 1)



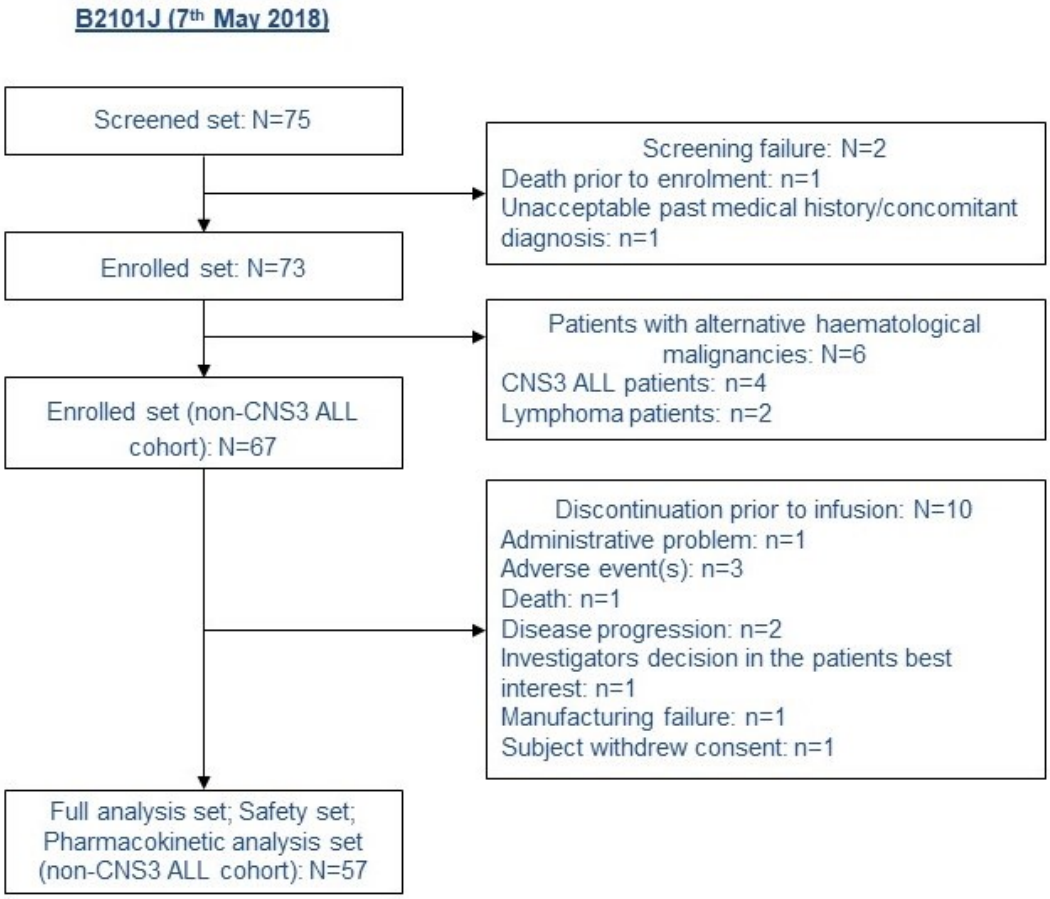
Cohort 1 was planned to include patients who were at very high risk at first relapse. Enrolment to Cohort 1 was terminated as patient enrolment was low. The single patient included in Cohort 1 was not included in the analysis.
Source: ELIANA CSR (DCO: 17th Nov 2022).

Figure 3: CONSORT diagram of patient flow for ENSIGN (reproduced from company's clarification response, Figure 2)



Source: ENSIGN CSR (24th May 2019).

Figure 4: CONSORT diagram of patient flow for B2101J (reproduced from company's clarification response, Figure 3)



Source: B2101J CSR (7th May 2018).

Study quality of tisagenlecleucel studies

The results of a critical appraisal of the three tisagenlecleucel studies[34-36] are presented in the CS[9] (Section B.2.5) using the GRACE checklist.[40] ELIANA and ENSIGN met most criteria for appropriate conduct and reporting, though all three studies scored "No" on the criterion "Were important confounding and effect-modifying variables taken into account in the design and/or analysis?" The EAG therefore considers that it is important to consider the generalisability of the study populations when applying the results to clinical practice or when comparing against studies of comparator treatments. The B2101J study also scored "No" on the following criteria: "Were the primary outcomes adequately recorded?", "Was the primary clinical outcome(s) measured objectively?" and "Were any meaningful analyses conducted to test key assumptions on which primary results are based?" The EAG notes that ORR was determined by local investigator in B2101J, but by Independent Review Committee (IRC) assessment in ELIANA and ENSIGN. The results of a critical appraisal of two comparator studies are presented in the CS (Appendix D.1.8[39]) and are summarised in Section 4.8 of this report.

4.2.3 NHSE SACT data on patients in England treated during managed access period

The NHSE CDF Report[37] captures SACT data from patients receiving tisagenlecleucel in England during the managed access period (November 2018 to June 2023). Eligibility criteria were similar to those applied in the tisagenlecleucel studies. This included data on 121 patients aged up to 25 years. Results for the NHSE SACT dataset are presented in the following sections alongside data from the three tisagenlecleucel clinical studies, for ease of reference.

4.2.4 Baseline characteristics in tisagenlecleucel studies

Baseline patient characteristics in the three tisagenlecleucel studies,[34-36] as well as the NHSE SACT[37] dataset, are shown in Table 8. The company's clarification response[38] (question B8) states that baseline characteristics for the intention-to-treat (ITT) population, including those who did not receive tisagenlecleucel infusion, were not available for the latest data-cuts; the company therefore did not provide these. The median age was 11 to 13 years across all studies and the NHSE SACT dataset. Across the ELIANA, ENSIGN and B2101J studies, the performance status was over 80 in 84%, 92% and 93% respectively; the company's clarification response (question B10) states that the slight difference in performance scores between studies is unlikely to have impacted long-term outcomes. The proportion of patients who were PH+ve was 3-5% across the three clinical studies, and 13% in the NHSE dataset.

The proportion of patients with prior SCT was 61%, 44% and 65% across ELIANA, ENSIGN and B2101J,[34-36] giving 57% across the pooled data. The NHSE SACT dataset[37] reports that 42/121 (35%) had relapse post-SCT (up to June 2023), but also reports that based on Hospital Episode Statistics (HES) data (up to March 2023), 21/114 (18%) had SCT before tisagenlecleucel; it is unclear why this discrepancy exists, or what the true rate of prior SCT was within the NHSE dataset.

Across the three tisagenlecleucel studies, patients had a median of 3 prior lines of therapy. Across these three studies, 8% were primary refractory while 92% were either relapsed or chemo-refractory (i.e., refractory to chemotherapy in the relapsed setting). The company stated that a further breakdown of the 92%, i.e., whether patients were relapsed or refractory, was not available (see clarification response,[38] question B11). In the NHSE dataset,[37] 9% were primary refractory, 17% secondary refractory, 35% relapsed post-SCT, 26% 2nd+ relapse post-chemotherapy, and 13% relapsed and SCT-ineligible. In the NHSE dataset,[37] 35% of patients had received previous blinatumomab and 6% had received previous genetically modified T-cell immunotherapy.

Clinical advisors to the EAG considered that the patient characteristics in the tisagenlecleucel studies and the NHSE dataset were generally representative of patients in clinical practice in England. Possible exceptions were: that the NHSE dataset had a higher than expected proportion who were Ph+ve (13%), and that prior SCT rates varied across studies and were unclear in the NHSE dataset.

Table 8: Baseline characteristics (full analysis set; adapted from CS, Tables 7 and 20)

Characteristic	ELIANA (N=79)[a]	ENSIGN (N=64)	B2101J (N=57)[b]	Pooled (N=200)	NHSE SACT (N=121)
Demographics					
Age (years)					
Median	11.0	12.5	11.0	12.0	13
Min–Max	3–24	3–25	1–24	1-25	-
Age category (years), n (%)					
<10	32 (41)	20 (31)	26 (46)	-	42 (35)
≥10 to <18	33 (42)	34 (53)	25 (44)	-	-
≥18	14 (18)	10 (16)	6 (11)	-	-
10 to 14	-	-	-	-	31 (26)
15-19	-	-	-	-	29 (24)
20-25	-	-	-	-	19 (16)
Sex, n (%)					
Female	34 (43)	34 (53)	25 (44)	93 (47)	53 (44)
Male	45 (57)	30 (47)	32 (56)	107 (53)	68 (56)
Karnofsky/Lanksy performance status, n (%)					
100	30 (38)	18 (28)	38 (67)	-	-
90	23 (29)	28 (44)	10 (18)	-	-
80	13 (17)	13 (20)	5 (9)	-	-
70	8 (10)	2 (3)	3 (5)	-	-
60 or less	5 (6)	3 (5)	-	-	-
Disease history and prior therapies					
Philadelphia chromosome positive (Ph+ve)[d]					
Yes	2 (3)	2 (3)	3 (5)	7 (4)	16 (13%)
Prior haematopoietic stem cell transplant (SCT)					
Yes	48 (61)	28 (44)	37 (65)	113 (57)	42/121 (35%) relapsed post-SCT; 21/114 (18%) prior SCT via HES data
Disease status, n (%)					
Primary refractory	6 (8)	7 (11)	3 (5)	16 (8)	11 (9)
Chemo-refractory or relapsed	73 (92)	57 (89)	54 (95)	184 (92)	-
Secondary refractory	-	-	-	-	20 (17)
Any relapse post-SCT	-	-	-	-	42 (35)
2nd+ relapse post chemotherapy	-	-	-	-	31 (26)
Relapsed and SCT-ineligible as comorbid	-	-	-	-	16 (13)
Previous lines of therapy, n (%)					
Median (min-max)	3 (1-8)	3 (1-9)	4 (1-8)	3 (1-9)	-
Time from initial diagnosis to first relapse (months)[c]					
Mean (min-max) [n]	33 (1-70) [n=73]	34 (1-108) [n=56]	-	-	-
Time from most recent relapse to tisagenlecleucel infusion (months)[c]					
Mean (min-max) [n]	4 (2-14) [n=73]	3 (1-10) [n=57]	6 (1-21)	4 (1-21)	-
Previous specific therapies					
Previous blinatumomab	-	-	-	-	42 (35)
Previous genetically modified T-cell immunotherapy	-	-	-	-	7 (6%)

[a] Data for disease history and prior therapies for ELIANA derived from ELIANA CSR (13th Apr 2018); [b] Data for B2101J presented refer to the non-CNS3 ALL cohort only; [c] Calculated for relapsed patients only; [d]From clarification response question B9

Allo-SCT - allogeneic stem cell transplantation; ALL - acute lymphoblastic leukaemia; CNS - central nervous system; MRD - minimal residual disease; NR - not reported; SCT - stem cell transplantation; SD - standard deviation.

Sources: ELIANA CSR (DCO: 17th Nov 2022); ELIANA CSR (DCO: 13th Apr 2018); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018); Laetsch et al. (2022)

4.3 Pooling of tisagenlecleucel studies

4.3.1 Rationale for pooling the tisagenlecleucel studies

Section B.2.8 of the CS[9] states that, for the purposes of increasing the overall sample size for tisagenlecleucel, data on EFS and OS from all three tisagenlecleucel studies[34-36] were pooled. This was conducted via simple pooling whereby the data from all patients were treated as if from a single study. The EAG considers this method of pooling to be reasonable.

4.3.2 Consideration of study similarity for pooling

The CS[9] (Section B.2.8) provides a consideration of whether the three studies[34-36] were sufficiently similar to justify pooling. In terms of study design, the CS (Section B.2.8) states that *"All three trials followed almost identical study designs"*.

In terms of intervention and dose, the CS[9] (Section B.2.8) states that *"The only difference for B2101J was the dosing regimen: in ELIANA and ENSIGN, patients received a single infusion with a narrower target dose range whereas in the B2101J study, patients were treated according to a dose escalation protocol, with a wider target dose range, and could therefore receive multiple infusions… the median dose received across all three trials was of the same magnitude and therefore this difference was not expected to bias the pooled estimate of efficacy for tisagenlecleucel."* The company's clarification response[38] (question B7) states that the dose escalation approach in B2101J was unlikely to have impacted on clinical outcomes.

In terms of outcome definitions, the CS[9] (Section B.2.8) states that *"The definitions of EFS and OS, the key outcome measures informing the economic analysis, were identical across all three trials."*

In terms of patient baseline characteristics, the CS[9] (Section B.2.8) states that *"Overall, it was considered that any differences between baseline characteristics were minor, and therefore it was considered appropriate to pool the data from all three trials"*.

Given the considerations above, the EAG considers that pooling data from the three tisagenlecleucel studies is appropriate. The EAG's clinical advisors also considered that the three studies were sufficiently similar to allow pooling. In the remainder of the clinical section of this report, pooled data are presented alongside the data for individual studies, for ease of reference.

4.4 Effectiveness of tisagenlecleucel

4.4.1 Response outcomes for tisagenlecleucel

Response outcomes from all three tisagenlecleucel studies are provided in Table 9 (based on CS,[9] Section B.2.6 and clarification response,[38] question B14). The EAG notes that ORR was determined by local investigator in B2101J, but by IRC assessment in ELIANA and ENSIGN, as discussed in Section

4.2.2. Pooled data were not presented for response outcomes in the CS, and response outcomes were not reported for the NHSE dataset. Across the three tisagenlecleucel studies, the ORR (defined as CR or CRi) was 82%, 70% and 95% across ELIANA, ENSIGN and B2101J, while the ORR with bone marrow MRD<0.01% was 81%, 67% and 86%, and the proportion with CR was 62%, 59% and 74%. The median duration of remission was 47 months, not reached, and 28 months.

Table 9: Summary of response outcomes in ELIANA, ENSIGN and B2101J (adapted from CS, Table 12 and clarification response, Table 7)

n (%)	ELIANA (N=79)[a]	ENSIGN (N=64)	B2101J (N=57)[b]
Best Overall Response (BOR)[c]			
ORR (CR+CRi)	65 (82%)	45 (70%)	54 (95%)
ORR with bone marrow MRD negative (i.e. MRD <0.01%)	64 (81%)	43 (67%)	49 (86%)
CR	49 (62%)	38 (59%)	42 (74%)
CRi	16 (20%)	7 (11%)	12 (21%)
NR	7 (9%)	13 (20%)	3 (5%)
Unknown	7 (9%)	6 (9%)	0
DoR (/RFS)			
Median	47 months	NE	28 months
% event free at 6 months	81	80	74
% event free at 12 months	67	71	61
% event free at 60 months	49	-	45

[a]Primary endpoint analysis (best overall response) was not repeated in ELIANA CSR (DCO: 17th Nov 2022); data for ELIANA primary efficacy refer to interim analysis in the ELIANA CSR (DCO: 13th Apr 2018) and presented in Grupp et al. 2019.
[b]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[c]BOR is reported within 3 months, 6 months and 28 days of tisagenlecleucel respectively for ELIANA, ENSIGN and B2101J.
BOR - best overall response; CI - confidence interval; CR - complete remission; Cri - CR with incomplete blood count recovery; DoR - duration of remission; FAS - full analysis set; MRD - minimum residual disease; NE - not estimable; NR - not reported; ORR - overall remission rate
Sources: ELIANA CSR (13th Apr 2018); ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018); Grupp et al. (2019); Laetsch et al. (2023); Grupp et al. (2018).

4.4.2 Event-free survival (EFS)

EFS for all three tisagenlecleucel studies[34-36] and for the pooled dataset is provided in Table 10 (based on CS,[9] Section B.2.6 and clarification response,[38] question B14). The Kaplan-Meier plots for EFS for all three studies and for the pooled dataset are shown in Figure 5 (without censoring for allo-SCT) and in Figure 6 (with censoring for allo-SCT). The EAG notes that both EFS plots and all EFS analyses are censored for receipt of further therapy. These plots are taken from the company's clarification response (question B15). Separate plots for the individual studies are presented in Section B.2.6 of the CS, but are not reproduced here. The median EFS (with censoring for allo-SCT) in ELIANA, ENSIGN and B2101J was 24 months, 16 months and 25 months, with a pooled EFS of 21 months. Results for EFS without censoring for allo-SCT appeared similar. However, results for EFS without censoring for further therapy were not available.

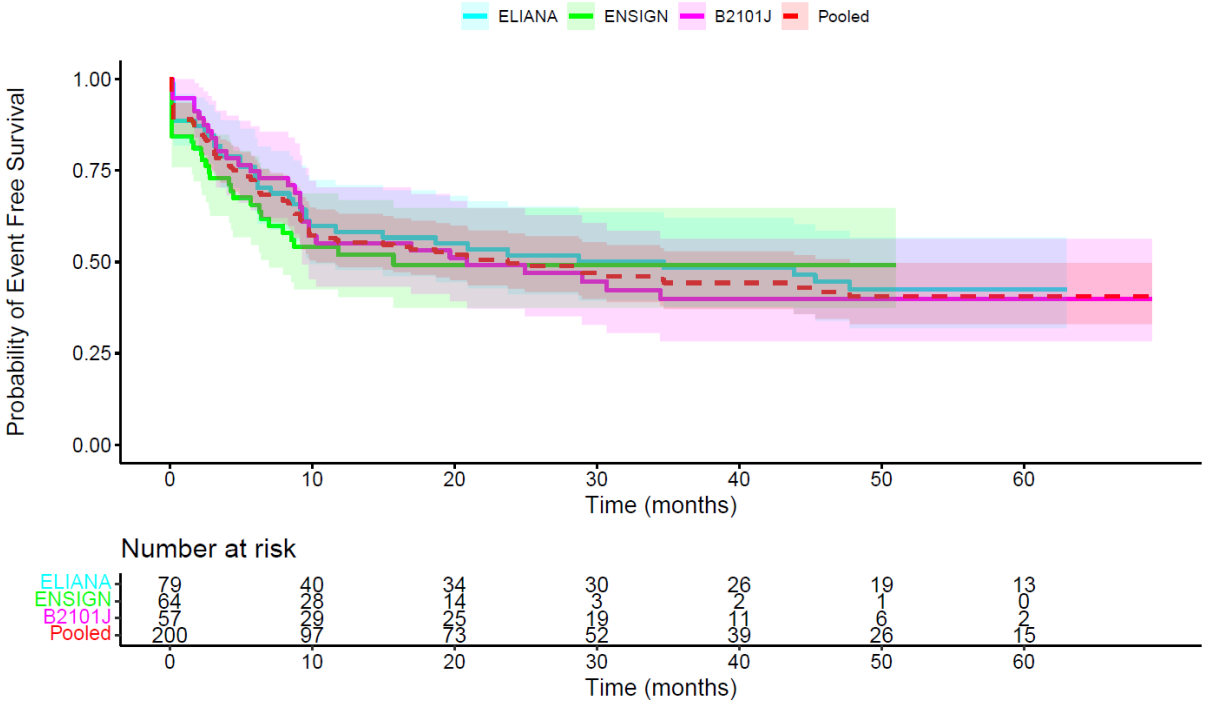
As noted in Section 4.2.2, a recent national UK analysis of real-world outcomes for 128 children and young adults who received tisagenlecleucel[45] presented results for both ELIANA-defined EFS and stringent EFS. Events in ELIANA-defined EFS included: death, relapse, or failure to respond by day 30, censoring patients receiving further therapy. Events in stringent EFS included: death, molecular or frank relapse, treatment failure, or further therapy. For ELIANA-defined EFS, the median was 22 months, with EFS of 71% and 50% at 1 and 2 years, respectively. For stringent EFS, the median was 7 months, with EFS of 45% and 38% at 1 and 2 years, respectively.[45] For completeness, these data are presented alongside the results of the tisagenlecleucel studies in Table 10.

Table 10: Summary of EFS and OS in ELIANA, ENSIGN and B2101J (adapted from CS, Table 12 and clarification response, Table 7)

n (%)	**ELIANA (N=79)**	**ENSIGN (N=64)**	**B2101J (N=57)[a]**	**Pooled (N=200)**	**NHSE SACT (N=121)**	**UK analysis (N=128)**	
EFS (censored for further therapy including SCT)						**EFS as in ELIANA**	**Stringent EFS**
Median	24 months	16 months	25 months	21 months	-	22 months	7 months
Number of events (%)	38/79 (48)	28/64 (44)	27/57 (47)	93/200 (47)	-	-	-
% event free at 6 months	72	67	74	72	-	-	-
% event free at 12 months	57	54	58	56	-	71	45
% event free at 24 months	50	48	50	49	-	50	38
% event free at 30 months	48	48	45	46	-	-	-
% event free at 60 months	42	-	43	41	-	-	-
OS							
Median	NE	30 months	48 months	48 months	NE	-	-
Number of deaths (%)	33/79 (42)	30/64 (47)	27/57 (47)	90/200 (45)	29/121 (24%)	-	-
% at 6 months	89	84	86	87	90	-	-
% at 12 months	77	65	79	74	81	-	-
% at 24 months	68	55	65	63	72	-	-
% at 30 months	65	49	61	60	-	-	-
% at 36 months	-	-	-	-	67	-	-
% at 60 months	56	-	47	47	-	-	-

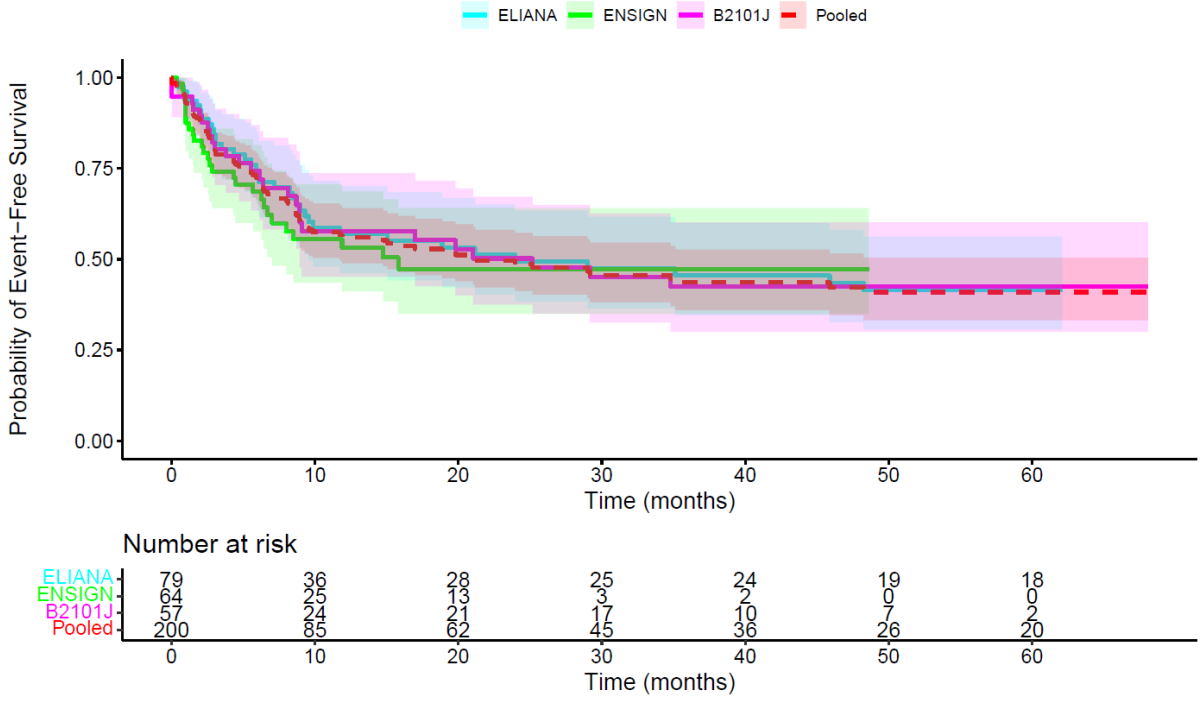
[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
BOR - best overall response; CI - confidence interval; CR - complete remission; Cri - CR with incomplete blood count recovery; DOR - duration of remission; FAS - full analysis set; MRD - minimum residual disease; NE - not estimable; NR - not reported; ORR - overall remission rate
Sources: ELIANA CSR (DCO: 13th Apr 2018); ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018); Grupp et al. (2019); Laetsch et al. (2023); Grupp et al. (2018).

Figure 5: Kaplan-Meier plot for EFS without censoring for allo-SCT, but censored for other subsequent therapies (reproduced from clarification response, Figure 7)



allo-SCT - allogeneic stem cell transplantation; EFS - event-free survival.
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN (DCO: 24th May 2019); B2101J (DCO: 7th May 2018).

Figure 6: EFS Kaplan-Meier plot with censoring for allo-SCT and other therapies (reproduced from clarification response, Figure 6 and replacing CS, Figure 20)

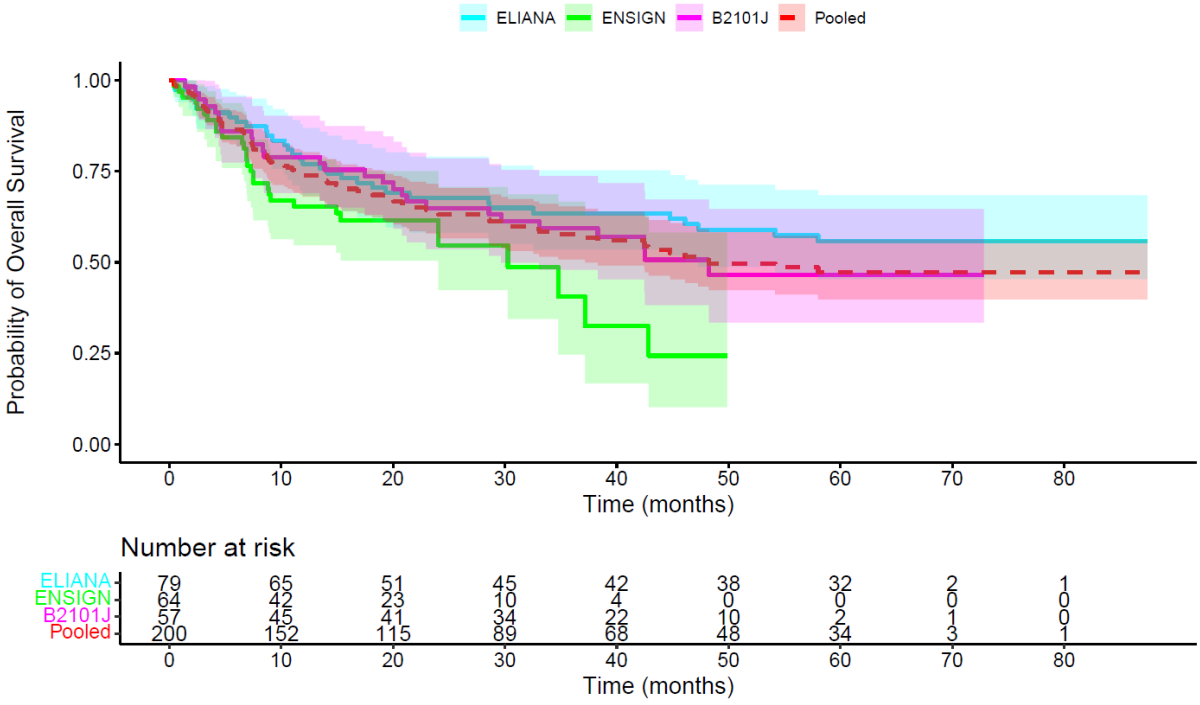


allo-SCT - allogenic stem cell transplantation; CS - company submission; EFS - event-free survival.
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN (DCO: 24th May 2019); B2101J (DCO: 7th May 2018).
This figure was provided in the company's clarification response (question B15) to replace Figure 20 in the CS, because Figure 20 included deaths after censoring due to allo-SCT, whereas this figure censors for allo-SCT regardless of later deaths, and is therefore consistent with the individual study plots in the CS.

4.4.3 Overall survival (OS)

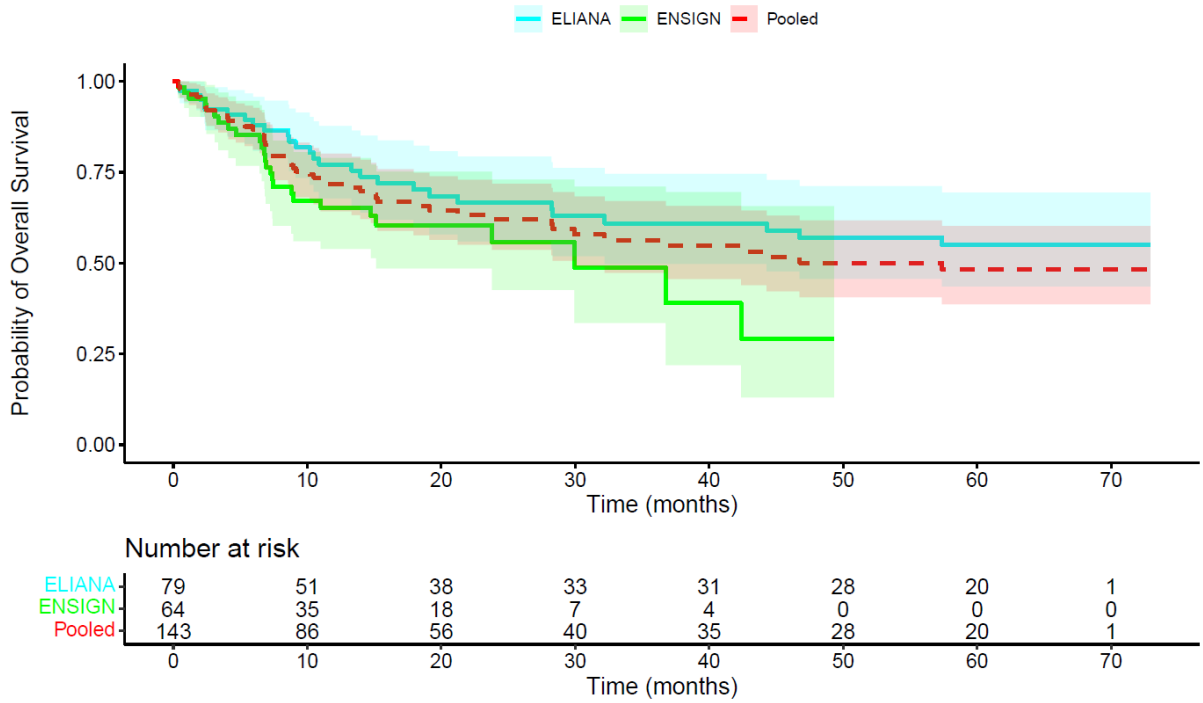
OS for all three tisagenlecleucel studies[34-36] and for the pooled dataset is provided in Table 10 (based on CS,[9] Section B.2.6 and clarification response,[38] question B14). The Kaplan-Meier plots for OS for all three studies and for the pooled dataset are shown in Figure 7 (without censoring for allo-SCT) and in Figure 8 (with censoring for allo-SCT). These are taken from the company's clarification response (question B21). Separate plots for the individual studies are presented in Section B.2.6 of the CS, but are not reproduced here. The Kaplan-Meier plot for OS for the NHS SACT[37] dataset is shown in Figure 9. The company's clarification response (question B19) notes that disease relapse following initial response appears to be the principal driver of late events seen in ENSIGN. As shown in Table 10, the median OS (without censoring for allo-SCT) was not reached in ELIANA, 30 months in ENSIGN and 48 months in B2101J. The median OS in the pooled dataset was 48 months. The OS at 2 years was 63% across the three pooled studies, and 72% in the NHSE SACT dataset (Table 10).

Figure 7: Kaplan-Meier curve for OS without censoring for subsequent allo-SCT (reproduced from CS, Figure 21 and clarification response, Figure 12)



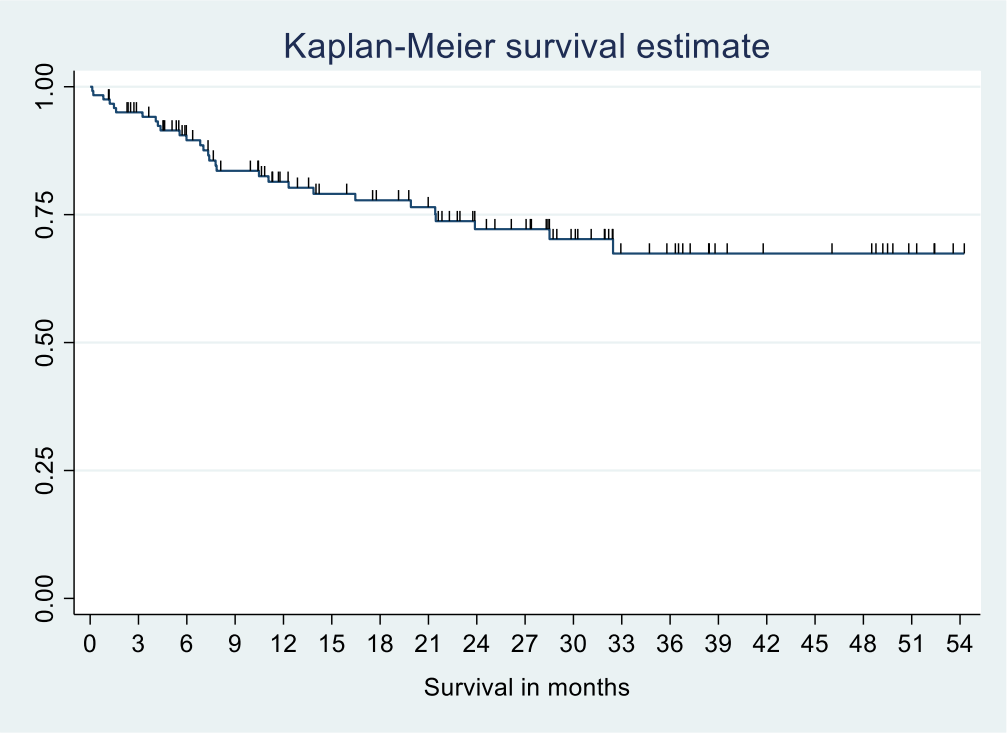
allo-SCT - allogeneic stem cell transplantation; OS - overall survival.
Footnote: B2101J was not included in this plot as no data for OS without censoring were available.
Sources: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019; B2101J DCO: 7th May 2018).

Figure 8: Kaplan-Meier curve for OS with censoring for subsequent allo-SCT (reproduced from clarification response, Figure 13)



allo-SCT - allogeneic stem cell transplantation; OS - overall survival.
Footnote: B2101J was not included in this plot as no data for OS with censoring were available from this study.
Sources: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019).

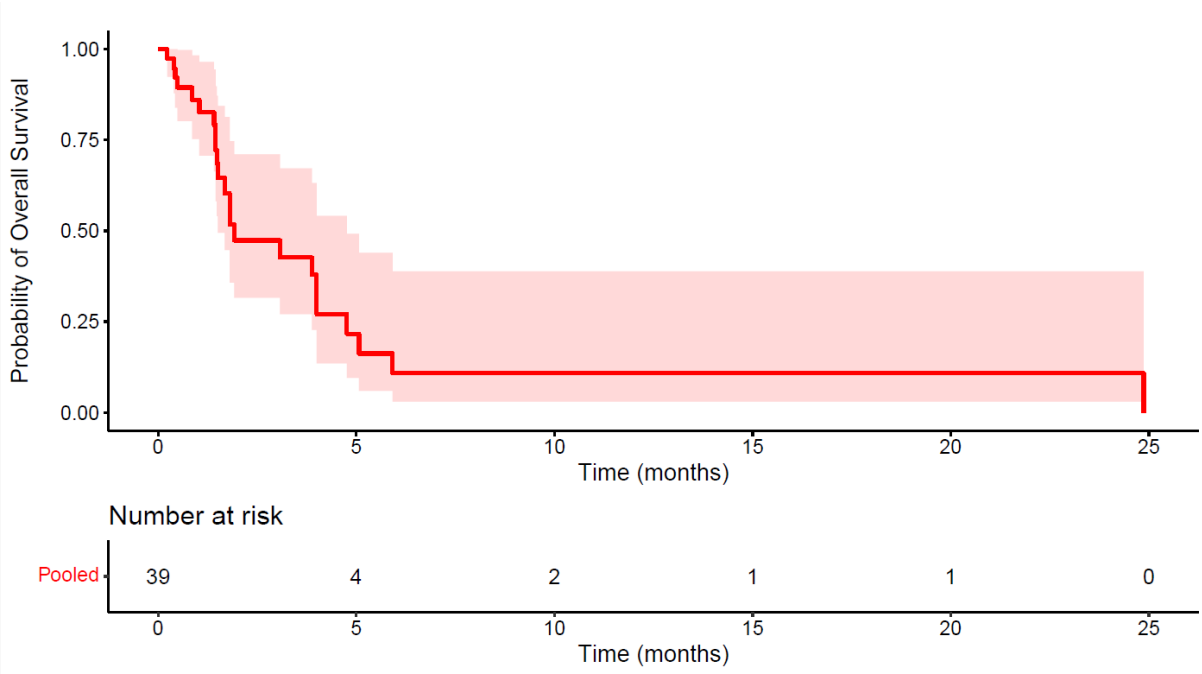
Figure 9: Kaplan-Meier curve for OS in NHSE SACT dataset (N=121, median follow-up 18 months)



4.4.4 Overall survival for patients not infused with tisagenlecleucel

OS for patients enrolled but not successfully infused with tisagenlecleucel in the three studies (based on earlier data cut-offs) is provided in the clarification response[38] (question B20). Median OS was 1.9 months in ELIANA, 1.5 months in ENSIGN and not estimable in B2101J. The pooled Kaplan-Meier curve is shown in Figure 10.

Figure 10: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel for pooled dataset (reproduced from clarification response, question B20, Figure 11)



OS - overall survival
Sources: Novartis Data on File (2023; ELIANA DCO: 31st Dec 2017, ENSIGN DCO: 24th May 2019, B2101J DCO: 30th Jan 2017).

4.4.5 Subgroup analyses for ORR

Subgroup analyses are presented in Section B.2.7 of the CS[9] for ORR only, not for EFS or OS. The CS states that ORR was consistently ≥60% across all subgroups evaluated in all three studies.

4.4.6 Patient-reported outcomes (PROs) in ELIANA

Section B.2.6.2 of the CS[9] reports patient-reported outcomes (PROs) for ELIANA[34] only. PROs were assessed in patients ≥8 years old only, via the paediatric quality of life (PedsQL) questionnaire and the EQ-5D (the EQ-5D-3L was used for patients aged ≥13 and the EQ-5D-Y was used for patients aged 8-12 years). The CS reports that PedsQL and EQ-VAS showed clinically meaningful improvements from baseline at all timepoints up to month 60, in patients achieving CR/CRi. Results for the full analysis set were similar; however, this analysis consisted mainly of patients with CR/CRi, since patients who did not respond to tisagenlecleucel mostly discontinued from the study and did not have a post-baseline

PRO assessment (clarification response,[38] question B17). Therefore, there were improvements in PROs in patients with a response to tisagenlecleucel, but little data on PROs in those who did not respond.

4.4.7 Rates of allo-SCT

The proportion of patients who received allo-SCT in the tisagenlecleucel studies and the pooled analysis is shown in Table 11, along with patients' disease status at the point of receipt of allo-SCT (based on data provided in clarification response,[38] question B25). In the tisagenlecleucel studies, the proportion receiving subsequent SCT was 23% in ELIANA,[34] and 14% in ENSIGN[35] and 14% in B2101J.[36] Across the pooled dataset, there were 37 SCTs given to 35 of 200 (18%) patients. The company states that 16% of patients had an SCT whilst in CR and 2% whilst in relapsed disease. However, as discussed in Section 4.2.2, the EAG's clinical advisors stated that the definition of EFS in the tisagenlecleucel studies, combined with censoring for allo-SCT, means it is unclear whether any patients classed as CR at the time of SCT may have had MRD positivity or B-cell recovery, which could be considered as events.

The proportion of subsequent SCTs in the NHSE SACT dataset[37] was reported as 13/114 (11%), using HES data on patients up to 31 March 2023 (Table 11). However, the EAG questions the reliability of this estimate, given the lack of clarity regarding the proportion of prior SCTs in this dataset (see Section 4.2.4).

Table 11: Allo-SCT rates in infused patients in ELIANA, ENSIGN, B2101J, pooled dataset and NHSE SACT data

n (%)		ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)	Pooled dataset (N=200)	NHSE SACT (N=114)[b]
Patients receiving subsequent allo-SCT		18 (23)[a]	9 (14)	8 (14)	35 (18)[a]	13 (11)[b]
Disease status at allo-SCT	**CR**	16 (20)[a]	8 (13)	7 (12)	31 (16)[a]	-
	RD	4 (5)[a]	0 (0)	0 (0)	4 (2)[a]	-
	Unknown	0	1 (2)	1 (2)	2 (1)[a]	-

[a]Two patients in the ELIANA trial received allo-SCT twice following tisagenlecleucel. Of which, one patient received both rounds of allo-SCT in CR and the other patient received the first round of allo-SCT in CR and the second round allo-SCT in RD.
[b]The NHSE SACT data[37] for SCT rates is based on HES data (up to 31 March 2023).
allo-SCT - allogenic stem cell transplant; CR - complete remission; DCO - data cut-off; RD - relapsed disease.
Sources: Novartis Data on File (2023; ELIANA DCO: 17th Nov 2022, ENSIGN DCO: 24th May 2019, B2101J DCO: 7th May 2018.

4.5 Safety of tisagenlecleucel

4.5.1 Studies providing safety data on tisagenlecleucel and safety cohorts

Safety was evaluated in all three tisagenlecleucel studies[34-36] (CS,[9] Section B.2.10). The safety population included all patients who received at least one infusion of tisagenlecleucel. Key safety data are summarised below.

4.5.2 Overview of safety of tisagenlecleucel

A summary of safety data is provided in Table 12. The overall frequency of AEs suspected to be study drug-related was 95-100% across studies. Serious AEs (SAEs) occurred in 80-91%, while SAEs suspected to be study drug-related occurred in 67-86%. Grade 3-4 AEs occurred in 91-97%, while Grade 3-4 AEs suspected to be study drug-related occurred in 75-97%. SAEs and Grade 3-4 AEs were more common within 8 weeks post-infusion, though events still occurred after more than 8 weeks.

The EAG notes that the CS[9] (Section B.2.10) also states that pregnancy and immunogenicity were included in the safety assessment, but that no data on these aspects are presented in the CS.

Table 12: Overall summary of AEs in ELIANA, ENSIGN and B2101J (safety set; adapted from CS, Table 27)

Adverse event, n (%)	ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)[a]
Number of patients with at least one AE	79 (100)	64 (100)	57 (100)
Suspected to be study drug-related	75 (95)	62 (97)	57 (100)
Patients with serious or other significant events			
Any time post-tisagenlecleucel infusion			
SAE	63 (80)	52 (81)	52 (91)
SAE suspected to be study drug-related	53 (67)	46 (72)	49 (86)
Grade 3/4 AE	72 (91)	59 (92)	55 (97)
Grade 3/4 AE suspected to be study drug-related	59 (75)	52 (81)	55 (97)
Within 8 weeks post-tisagenlecleucel infusion			
SAE	54 (68)	46 (72)	-
SAE suspected to be study drug-related	52 (66)	44 (69)	-
Grade 3/4 AE	66 (84)	54 (84)	-
Grade 3/4 AE suspected to be study drug-related	56 (71)	49 (77)	-
>8 weeks post-tisagenlecleucel infusion			
	(N=74)	**(N=56)**	
SAE	31 (42)	24 (43)	-
SAE suspected to be study drug-related	6 (8)	8 (14)	-
Grade 3/4 AE	45 (61)	31 (55)	-
Grade 3/4 AE suspected to be study drug-related	15 (20)	14 (25)	-

[a]*Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.*
AE - adverse event; SAE - serious adverse event.
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018).

4.5.3 Deaths

Across ELIANA,[34] ENSIGN[35] and B2101J,[36] 42%, 47% and 47% of patients died (see Table 13). Of these, 7 deaths (3.5% across all studies) occurred within 30 days post-infusion, due to underlying disease progression (N=2), intracranial haemorrhage (N=1), embolic stroke (N=1), or not reported (N=3).

In ELIANA,[34] 3 deaths (3.8%) were potentially related to tisagenlecleucel infusion, including 1 within 30 days of infusion (intracranial haemorrhage with concurrent toxicity of thrombocytopenia and coagulopathy, in which underlying disease and comorbidities were possible contributory factors); and 2 deaths more than 30 days post-infusion (1 due to systemic mycosis and 1 due to viral encephalitis). No deaths due to tisagenlecleucel were reported in ENSIGN[35] or B2101J[36] (see clarification response,[38] question B26).

Table 13: Deaths in ELIANA, ENSIGN and B2101J (safety set)

Deaths, n (%)	**ELIANA (N=79)**	**ENSIGN (N=64)**	**B2101J (N=57)[a]**
Total deaths	33 (42)	30 (47)	27 (47)
Death within 30 days post-infusion	2 (2.5)	2 (3.1)	3 (5)[b]
Underlying disease progression	1 (1.3)	1 (1.6)	
Intracranial haemorrhage **(potentially related to tisagenlecleucel)**	1 (1.3)		
Embolic stroke		1 (1.6)	
Reasons not reported in CS			3 (5)
Death >30 days post-infusion	31 (39)	28 (44)	24 (42)[c]
Underlying disease progression	24 (30)	24 (38)	
Viral encephalitis **(potentially related to tisagenlecleucel)**	1 (1.3)		
Systemic mycosis **(potentially related to tisagenlecleucel)**	1 (1.3)		
Lung infection (bacterial pneumonia)	1 (1.3)		
Hepatobiliary disease	1 (1.3)		
Graft versus host disease (GVHD)	1 (1.3)		
Multiple organ dysfunction syndrome and COVID-19 infection	1 (1.3)		
Unknown reason	1 (1.3)		
Complications of transplant surgery		1 (1.6)	
Glioblastoma multiforme		1 (1.6)	
Seizure		1 (1.6)	
Sepsis		1 (1.6)	
Reasons not reported in CS			24 (42)

[a]*Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.*
[b]*In the B2101J trial, this refers to deaths within 30 days of the last infusion of tisagenlecleucel (no deaths occurred within 30 days of the first infusion).*
[c]*Value calculated based on 27 deaths post-tisagenlecleucel infusion, and three of these occurring within 30 days of the last infusion. Therefore, 24 occurred 30 days after the last infusion (42% of 57).*
All deaths during both study follow-up and survival follow-up are summarised.

4.5.4 AEs by type

The most common AEs (≥20% of patients), pooled across all three studies, are shown in Table 14 (a more complete table can be found in the company's clarification response,[38] question B26, Table 11, and AEs suspected to be related to tisagenlecleucel infusion in question B26, Table 13). The most frequent AEs were: cytokine release syndrome (CRS, 81%), decreased white blood cell count (57%), decreased neutrophil count (52%), hypogammaglobulinaemia (51%), vomiting (49%), febrile neutropenia (48%), headache (47%), decreased platelet count (47%), decreased appetite (46%), nausea (45%), diarrhoea (41%), increased aspartate aminotransferase (41%), increased alanine aminotransferase (40%) and pyrexia (40%).

4.5.5 Grade 3 and 4 AEs

The most common Grade 3 and Grade 4 AEs (Table 14) were: febrile neutropenia (43% and 6%), decreased neutrophil count (11% and 32%), CRS (19% and 23%), decreased white blood cell count (16% and 26%), decreased platelet count (9% and 20%), hypotension (9% and 16%), decreased appetite (21% and 1%), lymphopenia (10% and 10%), increased aspartate aminotransferase (14% and 6%) and increased alanine aminotransferase (17% and 2%).

Table 14: AEs in ≥20% of patients post-tisagenlecleucel infusion (adapted from clarification response, question B26, Table 11)

Preferred term	Pooled dataset (safety set) (N=200)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one AE	200 (100)	41 (21)	145 (73)
Cytokine release syndrome	162 (81)	37 (19)	46 (23)
White blood cell count decreased	113 (57)	32 (16)	52 (26)
Neutrophil count decreased	104 (52)	22 (11)	64 (32)
Hypogammaglobulinaemia	102 (51)	11 (6)	0
Vomiting	97 (49)	8 (4)	0
Febrile neutropenia	96 (48)	85 (43)	11 (6)
Headache	94 (47)	13 (7)	0
Platelet count decreased	94 (47)	18 (9)	40 (20)
Decreased appetite	91 (46)	42 (21)	2 (1)
Nausea	89 (45)	15 (8)	0
Diarrhoea	82 (41)	5 (3)	0
Aspartate aminotransferase increased	81 (41)	28 (14)	11 (6)
Alanine aminotransferase increased	80 (40)	34 (17)	4 (2)
Pyrexia	80 (40)	16 (8)	3 (2)
Hypotension	69 (35)	18 (9)	31 (16)
Cough	69 (35)	0	0
Tachycardia	59 (30)	4 (2)	2 (1)
Fatigue	57 (29)	1 (0.5)	0
Haemoglobin decreased	53 (27)	13 (7)	4 (2)
Anaemia	52 (26)	28 (14)	1 (0.5)
Lymphopenia	47 (24)	19 (10)	20 (10)
Abdominal pain	40 (20)	5 (3)	0
Hypokalaemia	39 (20)	17 (9)	3 (2)

AE - adverse event
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018).

4.5.6 Serious AEs (SAEs)

SAEs occurring in ≥5% of patients, pooled across all three studies, are shown in Table 15 (a more complete table can be found in the company's clarification response,[38] question B26, Table 12, and SAEs suspected to be related to tisagenlecleucel in question B26, Table 14). The most common SAEs were: CRS (69%), febrile neutropenia (40%), hypotension (19%), pyrexia (14%) and encephalopathy (10%).

Table 15: SAEs in ≥5% post-tisagenlecleucel infusion (adapted from clarification response, question B26, Table 12)

Preferred term	Pooled dataset (safety set) (N=200)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one SAE	167 (84)	74 (37)	80 (40)
Cytokine release syndrome	138 (69)	35 (18)	45 (23)
Febrile neutropenia	79 (40)	69 (35)	10 (5)
Hypotension	37 (19)	8 (4)	25 (13)
Pyrexia	27 (14)	3 (2)	0
Encephalopathy	19 (10)	15 (8)	0
Hypoxia	17 (9)	9 (5)	6 (3)
Acute kidney injury	12 (6)	7 (4)	4 (2)
Disseminated intravascular coagulation	10 (5)	5 (3)	0
Capillary leak syndrome	10 (5)	1 (0.5)	9 (5)

SAE - serious adverse event.
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018).

4.5.7 AEs of special interest

AEs of special interest (AESIs) are shown in Table 16. The company's clarification response[38] (question B26) states that none of the CRS events were fatal and were managed with the appropriate supportive care and systematic anti-cytokine therapy.

Table 16: AESIs in pooled dataset (safety set; adapted from clarification response, question B26, Table 15)

Preferred term	Pooled data (safety set)[a] (N=200)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least one event	142 (71)	44 (22)	72 (36)
CRS	162 (81)	37 (19)	46 (23)
Febrile neutropenia[b,c]	75 (38)	65 (33)	10 (5)
Hematological disorders including cytopenias (total)[d,e]	82 (41)	31 (16)	43 (22)
Infection (total)	145 (73)	53 (27)	19 (10)
Serious neurological adverse reactions (total)[f]	103 (52)	36 (18)	1 (0.5)
Tumour lysis syndrome	10 (5)	9 (5)	1 (0.5)
Hypogammaglobulinaemia	102 (51)	11 (6)	0
Secondary malignancies[e]	3 (2)	3 (2)	0

[a]For study B2101J, AESIs reported anytime were unavailable from CSR, therefore values have been informed by AE incidence as listed in Table 29 of CS.
[b]In ELIANA, febrile neutropenia was counted as part of the total incidence for hematological disorders including cytopenias.
[c]In ENSIGN, febrile neutropenia defined as part of hematopoietic cytopenias not resolved by Day 28.
[d]In ENSIGN, defined as hematopoietic cytopenias not resolved by Day 28.
[e]Does not include data for B2101J
[e]Not reported in total, reported by individual parameters (i.e. white blood cells, hemoglobin).
[f]Reported as nervous system disorders in B2101J
Sources: ELIANA CSR (DCO: 17th Nov 2022); ENSIGN CSR (DCO: 24th May 2019); B2101J CSR (DCO: 7th May 2018).

4.5.8 Cytokine release syndrome (CRS)

Section B.2.10 of the CS[9] provides some data on management of CRS across the three tisagenlecleucel studies.[34-36] These data have been summarised by the EAG in Table 17. In total, 81% patients had CRS,

40% had Grade 3-4 CRS and no cases were fatal. In addition, 39% of all patients were admitted to an intensive care unit (ICU) with CRS, 30% were treated with systemic anti-cytokine therapy, and 20%, 12% and 6% required high-dose vasopressors, invasive ventilation, and dialysis, respectively.

Table 17: CRS management

Deaths, n (%)	**Pooled (N=200)**
CRS	162 (81)
Grade 3-4 CRS	80 (40)
Fatal CRS	0
Admitted to ICU with CRS	78 (39)
Treated with systemic anti-cytokine therapy	60 (30)
Required high-dose vasopressors	40 (20)
Required invasive ventilation	24 (12)
Required dialysis	12 (6)

CRS - cytokine release syndrome; ICU - intensive care unit

4.6 Ongoing studies

Section B.2.11 of the CS[9] states that all three tisagenlecleucel clinical studies have been completed. The CS states that there is an ongoing long-term follow-up study on CAR-T therapies (PAVO; NCT02445222) aimed at collecting safety and efficacy data (follow-up of 15 years) on patients who have received CAR-T therapy, regardless of indication.

4.7 Indirect treatment comparison: Overview

Due to the single-arm nature of the tisagenlecleucel studies and the potential comparator studies, the company undertook a matching-adjusted indirect treatment comparison (MAIC). A MAIC was conducted only for OS, not for EFS. The results of a MAIC using only the ELIANA study[34] for tisagenlecleucel are presented in the CS[9] (Section B.2.9), while the results of a MAIC using the pooled tisagenlecleucel data are presented in CS Appendix D.1.9.[39] The comparators included in the MAIC were blinatumomab and salvage chemotherapy. The CS (Section B.2.9) presents a number of studies of each comparator, then selects for inclusion in the MAIC a study of blinatumomab (von Stackelberg *et al.*, 2016[15]) and a study of clofarabine (Jeha *et al.*[14], 2006), the latter being considered as a proxy for FLAG-IDA, as no relevant studies were identified for this regimen. In this EAG report, a critique of the studies included in the MAIC is provided in Section 4.8, a summary of statistical methods and results of the MAIC is provided in Section 4.9, and a critique of statistical methods is presented in Section 4.10.

4.8 Indirect treatment comparison: Critique of included studies

4.8.1 Identification of comparator studies

The company's SLR aimed to identify studies of comparator treatments for children and young adults with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. Full eligibility criteria are described in CS Appendix D.1.1[39] (Tables 13 and 14). The EAG considers the search

methods and inclusion criteria to be appropriate to identify relevant studies of comparator treatments. However, the rationale for the inclusion and exclusion of comparator studies described in Section B.2.9 of the CS[9] has substantial limitations, making it difficult for the EAG to verify whether study inclusion/exclusion was appropriate. This issue is discussed further below.

4.8.2 Tisagenlecleucel studies included in MAIC

The tisagenlecleucel studies are described in Section 4.2 of this report.

4.8.3 Blinatumomab studies included in MAIC

Identification of blinatumomab studies

The CS[9] (Section B.2.9) states that in the company's 2023 SLR update, 6 studies of blinatumomab in paediatric patients with R/R B-cell ALL were identified, but only two studies were deemed potentially relevant to the ITCs and economic modelling: (i) Gore *et al.* (2018),[46] which is a later publication of the single-arm international study (NCT01471782) reported in von Stackelberg *et al*. (2016)[15] identified in the company's original SLR; and (ii) RIALTO, a single-arm international expanded open-access study (NCT02187354) reported by Locatelli *et al*. (2022)[47] [the EAG notes that this appears to be incorrectly cited in the CS as Locatelli *et al*. (2022)[48]].

The CS[9] does not cite the other 4 studies of blinatumomab identified in the 2023 SLR update, or explain why they were not includable, so the EAG is unclear which 4 studies were excluded here. In addition, the CS does not state which studies of blinatumomab were identified in the 2018 SLR or the 2019 update, other than the study by von Stackelberg *et al*. (2016).[15] The EAG requested a table of studies considered for blinatumomab (see clarification response,[38] question B28); however, only the three publications (two studies) listed above were tabulated. Therefore, the EAG is unclear which studies of blinatumomab were excluded and whether these exclusions were appropriate. The EAG undertook some brief searching and identified a third single-arm study of blinatumomab in paediatric patients with R/R B-cell ALL: the NEUF single-arm international expanded open-access study reported within Locatelli *et al*. 2022.[49]

These three single-arm studies (von Stackelberg *et al.* 2016,[15] RIALTO[47] and NEUF[49]) are summarised in Table 18. The EAG also identified three RCTs of blinatumomab vs. chemotherapy in R/R ALL, two in children or young adults (Locatelli *et al.*, 2022[48] and Brown *et al.*, 2021[50]) and one in adults (the TOWER study, reported by Kantarjian *et al*., 2017[51]). None of the RCT study populations exactly match the decision problem, but they are summarised here for completeness (see Table 19) and are discussed below.

Blinatumomab single-arm studies: selection and characteristics

The company considered only one study, von Stackelberg *et al.* 2016,[15] to be relevant for inclusion in the ITC. The EAG considers all three single-arm studies (von Stackelberg *et al.* 2016,[15] RIALTO[47] and NEUF[49]) to be potentially relevant to the decision problem, though all have limitations (see Table 18).

The von Stackelberg *et al.*[15] study population is considered by the EAG to have less favourable characteristics than those of the tisagenlecleucel studies. As noted in the Evidence Review Group (ERG) report in TA554, the ELIANA and ENSIGN studies required patients to have ≥5% bone marrow blasts, whereas von Stackelberg *et al.* specified >25% bone marrow blasts. However, as shown in Table 24 of the CS, the proportions of patients with baseline blast counts >50% were similar across the ELIANA and von Stackelberg *et al.* studies (68% and 74% of patients, respectively). In addition, 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, and that the population was very high risk based on tumour load, multiple prior relapses and the short interval between latest treatment and start of blinatumomab. The TA554 guidance[19] states that *"the committee acknowledged that patients in von Stackelberg et al. may therefore have had more progressive disease at baseline than patients in the tisagenlecleucel studies"* and that *"patients in von Stackelberg et al. may have worse outcomes than would be expected for blinatumomab in clinical practice."* Section B.2.9 of the CS[9] states that *"feedback from UK clinical experts was that … patients in the blinatumomab trial were fitter based on the proportion refractory and those with >3 lines of prior therapy."*

Regarding RIALTO,[47] Section B.2.9 of the CS states that this study was excluded because it permitted previous treatment with blinatumomab, therefore some patients may have overlapped with the von Stackelberg *et al.* study.[15] However, only 5% of patients in RIALTO had prior blinatumomab so the maximum overlap was 5%. Therefore, the EAG does not consider this to be a valid reason for exclusion. The EAG also notes that the CS for TA554 included an earlier publication of RIALTO in a modelling scenario analysis. The NEUF study[49] is not mentioned in the CS for the current appraisal.

One of the EAG's clinical advisors highlighted that von Stackelberg *et al.*[15] and RIALTO[47] enrolled patients aged under 18 years, whereas the tisagenlecleucel studies included patients up to the age of 24 or 25 years. The advisor commented that older patients (>18 years of age) tend to have a worse disease biology and higher transplant-related mortality rate which may lead to some bias in OS outcomes for blinatumomab compared with tisagenlecleucel.

Blinatumomab studies: critical appraisal

The company presented a critical appraisal of the study by von Stackelberg *et al.*[15] using the GRACE checklist[40] (CS Appendix D.1.8[39]). The study scored "No" on the criteria "Were important covariates

that may be known confounders or effect modifiers available and recorded?" and "Were any meaningful analyses conducted to test key assumptions on which primary results are based?" The CS does not present formal critical appraisal of any other studies of blinatumomab. Based on the critical appraisal, but also on differences in study populations and characteristics discussed in the remainder of this section, the EAG suggest caution when indirectly comparing single-arm studies of tisagenlecleucel versus its comparators.

Blinatumomab single-arm studies: results

In terms of the results of single-arm studies, von Stackelberg *et al.*[15] and NEUF[49] had similar subsequent SCT rates (34% and 26% respectively) and similar median OS (7.5 months and 8.2 months respectively), while RIALTO[47] had a higher subsequent allo-SCT rate (53%) and longer median OS (14.6 months). The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after blinatumomab in clinical practice as 56.7%.

The EAG's clinical advisors considered that the subsequent SCT rate, and therefore the median OS, in RIALTO[47] are more representative of clinical practice than those in von Stackelberg *et al.*[15] and NEUF.[49]

Table 18: Clinical evidence for blinatumomab – single-arm studies (adapted from clarification response, Tables 17 and 18, with additional studies added by EAG)

Author, year, study Source	Study design Country	Population, N, Age	Interventions	Line of relapse	Prior allo-SCT	Median OS	Subsequent allo-SCT	Reasons in CS for not considering evidence as efficacy data source	EAG view on inclusion/ exclusion
von Stackelberg (2016);[15] Gore (2018)[46] NCT01471782 Source: Company SLR (2023, 2018)	• Single-arm phase I/II • International (26 centres, Europe + US)	• Children, R/R ALL, N=70 • Age <18y, median 8y	Blinatumomab	• 1st relapse after full salvage induction, 2nd+ relapse, relapse post-SCT, or refractory • 56% refractory • 3%, 44%, 41%, 11% with 0, 1, 2 or 3 previous relapses	• 57% prior allo-SCT	von Stackelberg: • Median OS 7.5mo Gore: • Median OS 7.5mo (all pts) • By prior SCT: 10.6mo (prior SCT); 4.3mo (no prior SCT)	von Stackelberg: • 34% (24/70) subsequent allo-SCT Gore: • 36% (25/70) subsequent allo-SCT	von Stackelberg (2016): • Included in company ITC Gore (2018): • Same study as von Stackelberg (2016), but data only reported by allo-SCT use before or after blinatumomab	• EAG agrees includable • Likely worse outcomes than in clinical practice due to patient characteristics and low subsequent SCT rate
RIALTO Locatelli (2022)[16] NCT02187354 Source: Company SLR (2023)	• Single-arm expanded open-access • International (16 centres, Europe + US)	• Children, R/R ALL, N=110 • Age <18y, median 8.5	Blinatumomab	• 2nd+ relapse, relapse post-SCT, or refractory • 55% 2nd+ relapse, 40% relapse post-SCT, 15% primary refractory, 21% refractory to reinduction [categories overlap]	• 41% prior allo-SCT	• Median OS 14.6mo (all pts) • By subsequent SCT: 1yr OS: 87% (blin + SCT) 29% (blin alone)	• 53% (58/110) subsequent allo-SCT	• Eligibility criteria of RIALTO permitted patients previously treated with blinatumomab, therefore some patients may have overlapped between the von Stackelberg (2016) and RIALTO studies	• EAG considers includable. Only 5% prior blinatumomab so any overlap likely small • Clinical advisors: subsequent SCT rate and OS broadly representative of clinical practice
NEUF Locatelli 2022[49] Source: EAG; not in CS	• Single-arm expanded open-access • International (Europe including UK)	• Children, R/R ALL, N=72 • Age <18y, median 10y	Blinatumomab	• Relapsed or refractory • 56% refractory, 44% relapsed • 18%, 35% and 47% had 0, 1 or 2+ prior salvage therapies	• 39% prior allo-SCT	• Median OS 8.2mo (all pts) • By prior SCT: 6.4 mo (prior SCT) 9.2 mo (no prior SCT)	• 26% (19/72) subsequent allo-SCT	• Not reported in CS	• EAG considers includable • Clinical advisors: Low subsequent SCT rate

ALL - acute lymphoblastic leukaemia; allo-SCT - allogenic stem cell transplant; NR - not reported; OS - overall survival; SLR - systematic literature review; TA - technology appraisal.
Sources: Gore et al. (2018); Locatelli et al. (2022); von Stackelberg et al. (2016).

Blinatumomab RCTs: Patient characteristics and results

The three RCTs of blinatumomab vs. chemotherapy identified by the EAG are shown in Table 19. The EAG considers that these studies do not entirely match the decision problem, but they are included here for completeness. The two RCTs in children or young adults (Locatelli *et al*., 2022[48] and Brown *et al.*, 2021[50]) are both in first relapse in patients without prior SCT (one in high-risk relapse, one in high- and intermediate-risk relapse). In Brown *et al.*,[50] blinatumomab or chemotherapy were given as consolidation post-reinduction chemotherapy. No patients had prior SCT in either trial, and in both trials, most/all patients had subsequent SCT. In this sense, neither trial matches the decision problem, and outcomes were likely better in these RCTs than in the studies with later lines of relapse and lower rates of subsequent SCT. The median OS for blinatumomab was not reached in either study at follow-up of 44 months and 35 months, while 4-years OS was 77% in Locatelli *et al*.[48] and 2-year OS was 71% in Brown *et al.*[50]

The TOWER RCT (Kantarjian *et al*., 2017[51]) assessed blinatumomab vs. chemotherapy in adults at various lines of relapse, and was the main source of evidence in the NICE appraisal of blinatumomab in adults (TA450). In the blinatumomab arm, 24% of patients had a subsequent allo-SCT, and the median OS among patients aged 18-34 years was 9.9 months.

Table 19: Clinical evidence for blinatumomab - RCTs (adapted from clarification response, Tables 17 and 18, with additional studies added by EAG)

Author, year, study, source	Study design Country	Population, N, Age	Interventions	Line of relapse	Prior allo-SCT	Median OS	Subsequent allo-SCT	Reasons in CS for not including	EAG view on inclusion/ exclusion
Locatelli (2022)[48] NCT02393859 Source: EAG; not in CS	• RCT, phase 3, open-label • International (47 centres in Europe, Israel and Australia)	• Children, R/RALL, N=111 • Age <18y, median: blin 6, chemo 5	Blinatumomab vs. chemotherapy (IntReALL)	• 1st high-risk relapse 100%	• None prior allo-SCT	• Median OS (at median FU 44 mo): Blin: not reached Chemo: approx 26 mo • 4-yr OS: blin 77%, chemo 49%	• Blin: 94% subsequent allo-SCT • Chemo: 68% subsequent allo-SCT	Not reported in CS	• Recent RCT • Population all 1st relapse with no prior SCT; most had subsequent SCT
Brown (2021)[50] AALL1331, NCT02101853 Source: EAG; not in CS	• RCT, phase 3 • International (detail NR)	• Children + young adults, R/R ALL, N=208 • Age 1-30, median: 9	Blinatumomab vs. chemotherapy (UKALLR3) Both given as consolidation post-reinduction chemotherapy. All had subsequent SCT	• 1st high- and intermediate-risk relapse 100%	• None prior allo-SCT	At median FU 35 mo: • Age 1-30: o Median OS: not reached o 2yr OS: blin 71%, chemo 58% • Age <18: o Median OS not reached o 2yr OS: blin 72%, chemo 61% • Age 18-30: o Median OS: blin not reached, chemo NR o 2yr OS: blin 66%, chemo 47%	• 100% subsequent allo-SCT	Not reported in CS	• Recent RCT • Population all 1st relapse with no prior SCT; treatments given as consolidation post-reinduction; all had subsequent SCT
TOWER Kantarjian (2017)[51] Source: EAG; not in CS	• RCT, phase 3, open-label • International (101 centres in 21 countries)	• Adults, R?RALL, N=405 • Age 18+, mean: 41 • Subgroup age 18-34, N=183	Blinatumomab vs. chemotherapy (various)	• Refractory 42% • 1st 28% • 2nd+ 12% • Post-SCT 18%	• 35% prior allo-SCT	• Age 18-34yr: blin 9.9mo; chemo 4.5mo • All pts: blin 7.7mo; chemo 4.0mo	• Blin: 24% subsequent allo-SCT • Chemo: 24% subsequent allo-SCT [No data by age]	Not reported in CS. Clarification response (question B28) states excluded as no separate data for patients aged <26 years	• Less relevant age group, though the age 18-34 subgroup may provide supportive data for the young adult population

ALL - acute lymphoblastic leukaemia; allo-SCT - allogenic stem cell transplant; NR - not reported; OS - overall survival; SLR - systematic literature review; TA - technology appraisal.
Sources: Locatelli *et al. (2022); Brown et al. (2021); Kantarjian et al. (2017).*

4.8.4 Salvage chemotherapy studies included in MAIC

Identification of salvage chemotherapy studies

Section B.2.9 of the CS[9] states that no studies of FLAG-IDA in the correct population were identified; therefore, other studies of salvage chemotherapy were sought as a proxy. The CS reports the studies of salvage chemotherapy identified in the 2018 and 2019 SLRs, but not for the 2023 SLR update. The CS states that in the 2023 SLR update *"no trials were identified for FLAG-IDA"*, but it is not clear whether any studies of salvage chemotherapy (other than FLAG-IDA) were identified in the 2023 SLR update. Therefore, the EAG is unclear which studies of salvage chemotherapy were excluded and whether any exclusions were appropriate. It was beyond the remit of the EAG to search for additional studies of salvage chemotherapy. The studies of salvage chemotherapy identified in the CS, and their reasons for inclusion/exclusion, are discussed below.

Salvage chemotherapy studies: selection and characteristics

The studies of salvage chemotherapy identified in the CS,[9] and the reasons for inclusion/exclusion, are summarised in Table 20. All were single-arm clinical studies or prospective cohort studies. The company considered only one study, Jeha *et al.* (2006),[14] to be relevant for inclusion in the indirect comparison. This study assessed clofarabine in 61 patients aged <21 with B-cell ALL (79%) or T-cell/other ALL (21%), at 2nd+ line relapse or refractory. The TA554 guidance[19] states *"The clinical experts explained that clofarabine monotherapy was not used in clinical practice in the NHS because of concerns over increased toxicity compared with other treatment options. However, they noted that the efficacy of clofarabine was similar to that of FLA(G)-IDA, so it was plausible that data from Jeha et al. for clofarabine could be used as a proxy for salvage chemotherapy …. The committee was aware of a submission from NHS England which stated that clinical practice had changed since the publication of Jeha et al., and that outcomes in the study were likely to be worse than in clinical practice because supportive care and the availability and speed of access to stem cell donors have since improved".* The EAG's clinical advisors for the current appraisal also stated that clofarabine is rarely used in practice due to toxicity and lack of efficacy.

The company excluded a further eight studies (Table 20) for the following reasons. One study of 242 patients receiving nelarabine +/- cyclophosphamide and etoposide (Kuhlen *et al.*, 2018)[52] was excluded by the company because all patients had prior SCT and 20% had extramedullary relapse. However, the TA554 guidance[19] states *"The committee accepted that both Jeha et al. and Kuhlen et al. had a number of limitations, but concluded that that it was appropriate to consider both studies in its decision-making."* The TA554 guidance also states that the ERG in that appraisal considered that *"the much larger sample size and longer follow-up [in Kuhlen et al.] provided a more reliable and robust dataset compared with Jeha et al."* The TA554 guidance also notes several differences in prognostic factors between Kuhlen *et al*. and the tisagenlecleucel studies. Factors which may lead to shorter survival in Kuhlen *et al*. include

a higher rate (100%) of previous allo-SCT; inclusion of patients (25% of cohort) having only palliative care rather than salvage chemotherapy; and inclusion of patients with T-cell ALL or whose disease has relapsed less than 6 months after allo-SCT. Factors which may lead to a longer survival in Kuhlen *et al*. include a higher proportion of patients in first relapse and the inclusion of patients with extramedullary relapse. The EAG for this appraisal agrees with this summary of key differences and considers that, overall, patients in Kuhlen *et al*. had a worse prognosis than those in the tisagenlecleucel studies, but that Kuhlen *et al*. remains potentially relevant for estimating the effectiveness of salvage chemotherapy alongside Jeha *et al*. One of the EAG's clinical advisors highlighted that the characteristics of patients in Jeha *et al.* are more similar to the tisagenlecleucel studies than Kuhlen *et al.*, but that the OS outcomes and allo-SCT rate in Kuhlen appear to be more representative of what would be expected for patients treated with FLAG-IDA in practice. The clinical advisor suggested that OS outcomes for patients receiving FLAG-IDA in clinical practice would likely lie between the OS reported in these two studies. This scenario is considered in the EAG's economic analyses (see Section 5.6).

One study of nelarabine (Zwaan *et al.*, 2017)[53] and one study of bortezomib plus chemotherapy (Bertaina *et al.*, 2017)[54] were excluded as the company did not consider these regimens a reasonable proxy for FLAG-IDA. The EAG is unclear whether these regimens are any less appropriate than clofarabine (in Jeha *et al*.[14]) for estimating the effectiveness of salvage chemotherapy. However, the EAG considers that Zwaan *et al.* should be excluded since included patients had either T-cell ALL or T-cell lymphoma.

Four studies of clofarabine combination therapy (Miano *et al.,* 2012,[55] Hijiya *et al.,* 2011,[56] Locatelli *et al.,*2009,[57] and Cooper *et al.,* 2013[58]) were excluded on the basis that only clofarabine monotherapy is licensed in the UK for paediatric patients. The EAG does not consider this as reasonable grounds for exclusion, since clinical advice to the EAG is that clofarabine monotherapy is not commonly used in this setting. The EAG agrees with the following statement in the ERG report for TA554:[19] *"The ERG considers these reasons unjustified and unwarranted."*

Two studies, one of clofarabine combination therapy (Locatelli *et al.,* 2009,[57] also covered above) and one of bortezomib plus VXLD (Messinger *et al.,* 2012).[59] were excluded because they had a median OS of 9 months while the company's clinical feedback indicated that OS with FLA-IDA would be around 3 months. The EAG concurs with the comment in the ERG report for TA554,[19] which states *"the ERG does not agree with the exclusion of these trials, given that there is no clinical evidence on OS with FLA-IDA"*.

In addition, the EAG identified three RCTs of blinatumomab vs. chemotherapy, described earlier in Table 19. As noted earlier, these do not entirely match the decision problem but are included here for

completeness. Furthermore, the ERG in TA554 identified a retrospective study by Sun *et al*. (2018)[60] of 325 children with R/R B-ALL. However this study did not report OS (only CR, and EFS in patients achieving CR), and was not discussed in the final guidance for TA554[19] or in the CS[9] for this appraisal, and so this study is not discussed further here.

In summary, the EAG is unclear whether the study of clofarabine by Jeha *et al.* (2006)[14] is any more relevant than the other studies listed in Table 20. In addition, as noted above, the EAG is unclear whether any further studies of salvage chemotherapy were published after 2019, as it is not clear from the CS[9] whether any such studies were identified in the company's 2023 SLR update. The TA554 guidance[19] states *"The committee accepted that both Jeha et al. and Kuhlen et al. had a number of limitations, but concluded that that it was appropriate to consider both studies in its decision-making"*. The EAG for this appraisal agrees that inclusion of both Jeha *et al.* and Kuhlen *et al.* is a pragmatic approach to estimating the effectiveness of salvage chemotherapy. The EAG's clinical advisors thought that OS for patients treated with FLAG-IDA would be better than the OS estimates reported by Jeha *et al.*

Salvage chemotherapy studies: critical appraisal

The company presented a critical appraisal of Jeha *et al.*[14] using the GRACE checklist[40] (CS Appendix D.1.8[39]). The study scored "No" on the criterion "Were any meaningful analyses conducted to test key assumptions on which primary results are based?" The CS does not present a formal critical appraisal of any other studies of salvage chemotherapy. Based on the critical appraisal, but also on differences in study populations and characteristics discussed in the remainder of this section, the EAG suggest caution when indirectly comparing single-arm studies of tisagenlecleucel versus comparators.

Salvage chemotherapy studies: results

In terms of results of the studies in Table 20, Jeha *et al.*[14] had a subsequent allo-SCT rate of 15% and median OS of 3 months, while Kuhlen *et al.*[52] had a subsequent allo-SCT rate of 26% and median OS of approximately 6 months. Of the remaining 5 studies (excluding Zwaan *et al.*[53] in which all patients had T-cell ALL or T-cell lymphoma), the subsequent SCT rates and median OS were as follows: 28% and 9 months;[57] 29% and 3 months;[58] 40% and 2.5 months;[56] 41% and 9 months;[59] 46% and 4.1 months;[55] and 49% and 13 months.[54] The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after salvage chemotherapy in clinical practice as 38.3%.

Regarding the RCTs of blinatumomab vs. chemotherapy identified by the EAG (Table 19), in the two RCTs in children or young adults at first relapse (within the chemotherapy arms), one (Locatelli *et al*., 2022[48]) had a subsequent SCT rate of 68% and median OS of approximately 26 months, while the other (Brown *et al*., 2021[50]) had a subsequent SCT rate of 100% and median OS was not reached (2-year OS

was 58%). These study populations likely have a more favourable prognosis than the population in the decision problem as patients were at first relapse and had not had prior SCT. In the TOWER RCT[51] in adults with R/R ALL, the subsequent SCT rate was 24%, and median OS was 4.5 months (for patients aged 18-34 years).

As noted above, the EAG considers that inclusion of both Jeha *et al*.[14] and Kuhlen *et al*.[52] is a pragmatic approach to estimating the effectiveness of salvage chemotherapy, though both studies are likely to underestimate the subsequent SCT rate. The EAG's clinical advisors suggested that the subsequent SCT rate and median OS in Jeha *et al.* were lower than would be expected in practice. One of the clinical advisors suggested that the OS reported by Kuhlen *et al.* would be more reflective of clinical practice, whereas another advisor thought that OS would lie between Jeha *et al.* and Kuhlen *et al.*

Table 20: Clinical evidence for salvage chemotherapy (from company 2018 and 2019 SLR; adapted from CS, Tables 21 and 22)

Author, year, design, country	Population, N Age	Intervention	Line of relapse	Prior allo-SCT	Mean OS	Subsequent allo-SCT	Reasons in CS for not considering evidence	EAG view on inclusion/ exclusion
Kuhlen (2018)[52] ALL-SCT 2003/2007 Prospective cohort study Austria	• N=242 • B-ALL 75%, T/other ALL 25% • Age ≤19 years • Median age at study entry 11 (2 to 19)	• Nelarabine alone or nelarabine + cyclophosphamide + etoposide (25% palliative therapy only)	• Any relapse post-SCT • 29%, 57%, 14% at 1st, 2nd and 3rd+ relapse	• 100% prior allo-SCT	• Median OS approx 6mo[a] [all pts + B-cell pts] • 3yr OS: 20% [all pts; NR for B-cell pts]	• 26% (61/232) subsequent allo-SCT [all pts]	• All prior SCT • 20% had extramedullary relapse	• EAG considers relevant • Large sample size and long follow-up (as noted in TA554) • Factors suggesting worse prognosis: all prior SCT; 25% palliative only; some T-cell; some short time to relapse • Factors suggesting better prognosis: 29% first relapse; 20% extramedullary relapse
Bertaina (2017)[54] Prospective cohort study Italy	• N=37 • B-ALL 81%, T-ALL 19% • Age ≤15 years at diagnosis and ≤21 years at treatment • Median age at study entry 7 (1-15)	• Bortezomib + chemotherapy	• Relapsed or refractory • 19% refractory • 41%, 30%, 11% had 1, 2 or 3+ previous relapses	• 41% prior allo-SCT	• Median OS approx 13mo [all pts + B-cell pts) • 2yr OS: 31% [all pts] 24% [B-cell]	• 49% (18/37) subsequent allo-SCT [all pts]	• Small sample size • Not considered reasonable proxy for FLAG-IDA	• EAG unclear whether bortezomib + chemotherapy is less relevant than clofarabine
Zwaan (2017)[53] Single-arm, study Germany + Netherlands	• N=28 • T-ALL 61%; T-cell lymphoma 39% • Age <21 years • Median age at study entry 12 (3 to 22)	• Nelarabine alone	• All 2nd+ relapse or refractory	• 11% prior allo-SCT	• Median OS 6.5mo [all T-cell]	• 46% (13/28) subsequent allo-SCT [all T-cell]	• Small sample size • Not considered reasonable proxy for FLAG-IDA	• EAG considers not relevant population (all T-cell, some lymphoma)
Cooper *et al.* (2013)[58] Single-arm clinical trial US/ Canada	• N=21 • B-ALL 71%, T/other ALL 29% • Age 1–21; age at initial diagnosis 6 (0.3–22) • Median age at study entry 12 (1–26)	• Clofarabine + cytarabine	• 2nd/3rd relapse or refractory • 86% in 2nd or 3rd relapse • 14% refractory to re-induction in first relapse	• 29% prior allo-SCT (excluded if within 12 months of study entry)	• Median OS approx 3mo [all pts]	• 29% (6/21) subsequent allo-SCT [all pts]	• Clofarabine combination therapy not licensed; clofarabine monotherapy is	• EAG unclear whether clofarabine combination is less relevant than clofarabine monotherapy

Author, year, design, country	Population, N Age	Intervention	Line of relapse	Prior allo-SCT	Mean OS	Subsequent allo-SCT	Reasons in CS for not considering evidence	EAG view on inclusion/ exclusion
Messinger *et al.* (2012)[59] Single-arm clinical trial US	• N=22 • B-ALL 91%, T-ALL 9% • Age at diagnosis <21; age >1 yr at study entry • Median age at study entry 12 (1–22)	• Bortezomib + VXLD	• 2nd or 3rd relapse • 77% at 2nd relapse; 23% at 3rd relapse	• 18% prior allo-SCT	• Median OS approx 9mo [all pts]	• 41% (9/22) subsequent allo-SCT [all pts]	• OS longer than expected for FLAG-IDA	• EAG considers not appropriate to exclude based on longer OS than expected
Miano *et al.* (2012)[55] Prospective cohort study Italy	• N=40 • ALL 60%, AML 40% • Age 1–20 years • Median age at diagnosis 5 (0.2–17); median age at study entry 8 (1–20)	• Clofarabine + cyclophosphamide + etoposide	• 2nd+ relapse or refractory • 17%, 38%, 38% and 8% with 0, 1, 2 and 3 prior relapses [ALL pts]	• 50% prior allo-SCT [ALL + AML]	• Median OS: 4.1mo [ALL+AML] Approx 3mo [ALL]	• 46% (11/24) subsequent allo-SCT [ALL only]; 38% (15/40) [ALL+AML]	• Clofarabine combination therapy not licensed; clofarabine monotherapy is	• EAG unclear whether clofarabine combination is less relevant than clofarabine monotherapy
Hijiya *et al.* (2011)[56] Single-arm clinical trial US	• N=25 • B-ALL 84%, T/other ALL 16% • Age at diagnosis 1–21 years • Median age at study entry 14 (1–21)	• Clofarabine + cyclophosphamide + etoposide	• 1st, 2nd or 3rd relapse or refractory • 16%, 56% and 28% with 1, 2, 3 prior regimens • 60% refractory to prior therapy (8% primary)	• 16% prior allo-SCT	• Median OS 2.5mo	• 40% (10/25) subsequent allo-SCT	• Clofarabine combination therapy not licensed; clofarabine monotherapy is	• EAG unclear whether clofarabine combination is less relevant than clofarabine monotherapy
Locatelli *et al.* (2009)[57] Non-randomised study Italy	• N=25 • B-ALL 68%, T-ALL 32% • Advanced ALL • Age at diagnosis ≤15; age at treatment 1–21 • Median age at diagnosis 8 (1–15); median age at study entry 13 (4–21)	• Clofarabine + cyclophosphamide + etoposide	• Refractory or multiple relapsed ALL • 24%, 8% at 2nd, 3rd relapse • 68% refractory to prior therapy	• 29% prior allo-SCT	• Median OS: Approx 9mo [B-cell] Approx 7mo [all pts] • 18mo OS: 20% [all pts] 33% [B-cell]	• 28% (7/25) subsequent allo-SCT [all pts]	• OS longer than expected for FLAG-IDA • Clofarabine combination therapy not licensed; clofarabine monotherapy is	• EAG considers not appropriate to exclude based on longer OS than expected • EAG unclear whether clofarabine combination is less relevant than clofarabine monotherapy

Author, year, design, country	Population, N Age	Intervention	Line of relapse	Prior allo-SCT	Mean OS	Subsequent allo-SCT	Reasons in CS for not considering evidence	EAG view on inclusion/ exclusion
Jeha (2006)[14] Single-arm clinical trial US	• N=61 • B-ALL 79%, T/other ALL 21% • Age at diagnosis <21 • Median age at study entry 12 (1– 20)	• Clofarabine	• All 2nd+ relapse or refractory • 57% refractory to last regimen • 38%, 62% had 2 and 3+ prior regimens	• 30% prior allo-SCT (25% one; 5% two)	• Median OS: 3mo [all pts]	• 15% (9/61) subsequent allo-SCT [all pts]	• Included	• TA554 and clinical advisors suggest clofarabine rarely used due to toxicity and lack of efficacy • Access to SCT was less available at time of study

[a]The median OS for Kuhlen et al. (2018)[52] of 7.7 months in CS Table 21 appears incorrect; this is the time from SCT to relapse prior to receiving salvage chemotherapy.
AIEOP - Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL - acute lymphoblastic leukaemia; allo-SCT - allogeneic stem cell transplantation; DFCI - Dana Farber Cancer Institute; EFS - event-free survival; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; G-CSF - granulocyte-stimulating colony factor; OS - overall survival; VXLD - Doxorubicin; SLR - systematic literature review.

4.9 Indirect treatment comparison: Summary of statistical methods and results

4.9.1 Overview of ITC methods

Owing to the single-arm nature of the studies of tisagenlecleucel and its comparators, the company adopted an unanchored MAIC approach. MAIC is a population adjustment method that makes use of the available individual patient data (IPD) to adjust for the baseline imbalances between the tisagenlecleucel studies and the comparator studies selected by the company (von Stackelberg *et al.*[15] and Jeha *et al.*[14]). Individuals in the IPD population from the tisagenlecleucel studies are weighted to match the patient characteristics of the comparator populations with the intention of deriving meaningful comparisons. The company has conducted four MAIC analyses to compare tisagenlecleucel based on two different datasets (pooled and ELIANA only) with two comparators (blinatumomab and salvage chemotherapy), respectively.

4.9.2 ITC using the pooled tisagenlecleucel data

In the MAIC analysis using the pooled data, all patients from the three tisagenlecleucel studies (ELIANA,[34] ENSIGN[35] and B2101J[36]) were included. Covariates that are potential effect modifiers were considered and the rank of importance for adjustment provided by the company is listed in Table 21. The company selected baseline characteristics to be included in the MAIC based on data availability and input from clinical experts, as well as making sure that the effective sample size (ESS) was at least 50% of the patient population.

In the comparison against blinatumomab, only two covariates - previous remissions/relapses and prior haematopoietic stem cell transplantation (HSCT) - were included in the MAIC analysis. There are still noticeable differences between the adjusted tisagenlecleucel population and the von Stackelberg population[15] in trisomy 21 (6.64% vs 2.86%), MLL total (3.70% vs 14.29%), months since last relapse (4.36 vs 2.90), hypodiploidy (2.21% vs 5.71%), blast count (61.13% vs 74.29%), age (11.87 vs 8.00) and sex (male, 52.51% vs 67.14%), as presented in Table 22. The EAG notes that trisomy 21 (available in both studies) is considered as an important covariate for adjustment based on Table 21 but it has not been adjusted for by the company.

In the comparison against salvage chemotherapy, only two covariates, number of prior lines of therapy and prior HSCT, were considered in the MAIC analysis. After adjustment, the mean of the two included covariates is balanced between the adjusted tisagenlecleucel population and the Jeha *et al.* population, as shown in Table 23. Differences still exist in the unadjusted covariates: BCR-ABL (1.33% vs 4.92%), hypodiploidy (1.79% vs 9.84%), age (11.94 vs 12.00) and sex (male, 52.08% vs 60.66%). It is unclear whether trisomy 21 (high importance for adjustment), months since last relapse (medium importance for adjustment), MLL total (medium importance for adjustment), and blast count (medium importance for adjustment) are balanced as these covariates are not reported in Jeha *et al*.[14]

Table 21: Baseline characteristics considered for inclusion in the MAIC (reproduced from CS, Table 23)

Characteristic	Rank
Trisomy 21	High
Number of previous remissions/relapses	High
Prior HSCT	High
Number of prior lines of therapy	High
MLL total	Medium
BCR-ABL	Medium
Months since last relapse	Medium
Hypodiploidy	Medium
Blast count	Medium
Age	Low
Sex	Low

BCR-ABL - breakpoint cluster region-Abelson; HSCT - haematopoietic stem cell transplant; MLL - mixed-lineage leukaemia.

Table 22: Summary of baseline characteristics of the pooled tisagenlecleucel data and von Stackelberg *et al.* (2016) before and after adjustment (reproduced from CS Appendix D, Table 19)

Characteristic	Adjusted for	Pooled tisagenlecleucel data		Comparator
		Before adjustment	After adjustment	von Stackelberg *et al.* (2016)
Trisomy 21 (%)	No	6.99	6.64	2.86
Previous remissions/relapses = 0 (%)	Yes	8.00	2.86	2.86
Previous remissions/relapses = 1 (%)	Yes	27.00	44.29	44.29
Previous remissions/relapses = 2 (%)	Yes	31.00	41.43	41.43
Previous remissions/relapses = 3+ (%)	Yes	34.00	11.43	11.43
Prior HSCT (%)	Yes	56.50	57.14	57.14
Number of prior lines of therapy (mean)	No	3.52	3.31	NR
MLL total (%)	No	2.50	3.70	14.29
BCR-ABL (%)	No	4.14	2.28	2.86
Months since last relapse (mean)	No	4.35	4.36	2.90
Hypodiploidy (%)	No	1.20	2.21	5.71
Blast count (%)	No	60.50	61.13	74.29
Age (mean)	No	12.03	11.87	8.00
Sex, male (%)	No	53.50	52.51	67.14

BCR-ABL - breakpoint cluster region-Abelson; HSCT - haematopoietic stem cell transplant; MLL - mixed-lineage leukaemia; NR - not reported.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] ENSIGN CSR (DCO: 24th May 2019);[35] B2101J CSR (DCO: 7th May 2018);[36] von Stackelberg et al. (2016).[15]

Table 23: Summary of baseline characteristics of the pooled tisagenlecleucel data and Jeha *et al.* (2006) before and after adjustment (reproduced from CS Appendix D, Table 20)

Characteristic	Adjusted For	Pooled tisagenlecleucel data		Comparator
		Before adjustment	After adjustment	Jeha *et al.* (2006)
Trisomy 21 (%)	No	6.99	6.65	NR
Previous remissions/relapses (mean)	No	2.12	1.72	NR
Prior HSCT (%)	Yes	56.50	29.50	29.51
Number of prior lines of therapy = 1 (%)	No	5.50	0.00	0.00
Number of prior lines of therapy = 2 (%)	Yes	25.50	37.71	37.70
Number of prior lines of therapy = 3 (%)	Yes	24.50	36.07	36.07
Number of prior lines of therapy = 4 (%)	Yes	19.50	21.31	21.31
Number of prior lines of therapy = 5 (%)	Yes	13.50	1.64	1.64
Number of prior lines of therapy = 6 (%)	Yes	11.50	3.28	3.28
MLL total (%)	No	2.50	3.22	NR
BCR-ABL (%)	No	4.14	1.33	4.92
Months since last relapse (mean)	No	4.35	4.05	NR
Hypodiploidy (%)	No	1.20	1.79	9.84
Blast count (%)	No	60.50	62.08	NR
Age (mean)	No	12.03	11.94	12.00
Sex, male (%)	No	53.50	52.08	60.66

BCR-ABL - breakpoint cluster region-Abelson; HSCT - haematopoietic stem cell transplant; MLL - mixed-lineage leukaemia; NR- not reported.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] ENSIGN CSR (DCO: 24th May 2019);[35] B2101J CSR (DCO: 7th May 2018);[36] Jeha et al. (2016).[14]

Histogram plots of rescaled weights for the comparisons with von Stackelberg *et al.*[15] and Jeha *et al.*[14] are presented in Figure 11 and Figure 12, respectively. Overall, the majority of the weights are between 0 and 2. In the comparison with von Stackelberg *et al.*, the largest weight is close to 2.5, and in the comparison with Jeha *et al.*, the largest weight is close to 3. The pooled dataset included 200 patients at baseline: more than 80 (40%) patients have weights close or equal to 0 in the comparison with von Stackelberg *et al*., and more than 40 (20%) patients have weights close or equal to 0 in the comparison with Jeha *et al.*

Figure 11: Distribution of weights of patients in the pooled tisagenlecleucel data in the comparison with von Stackelberg *et al.* (2016) (reproduced from CS Appendix D, Figure 2)

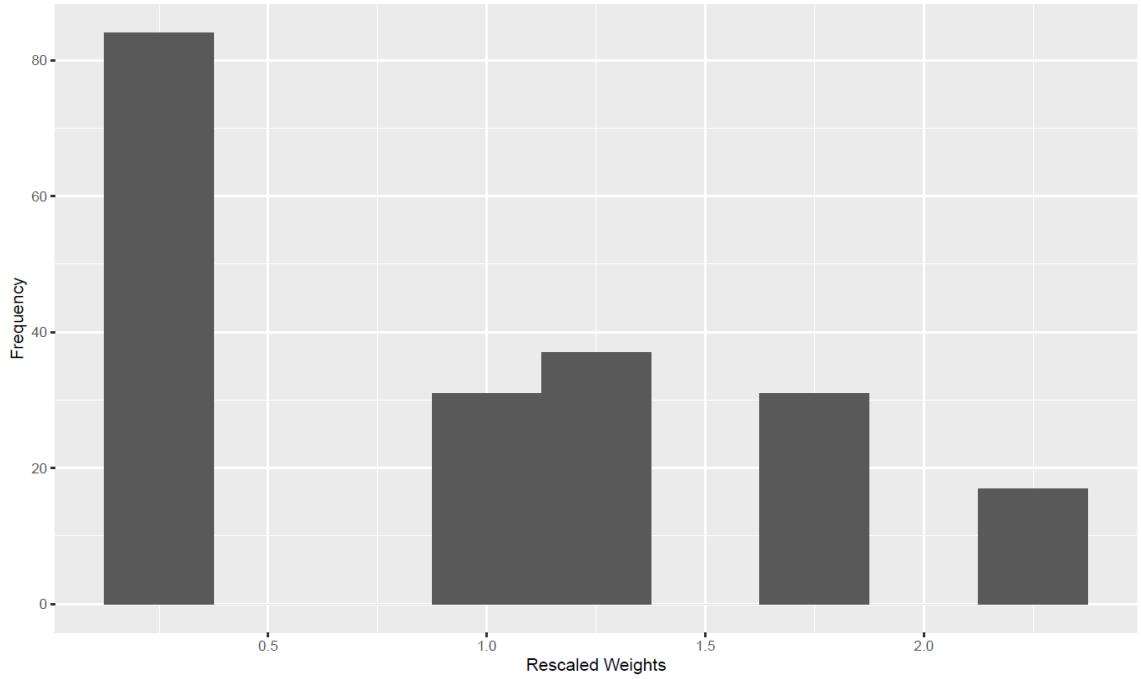
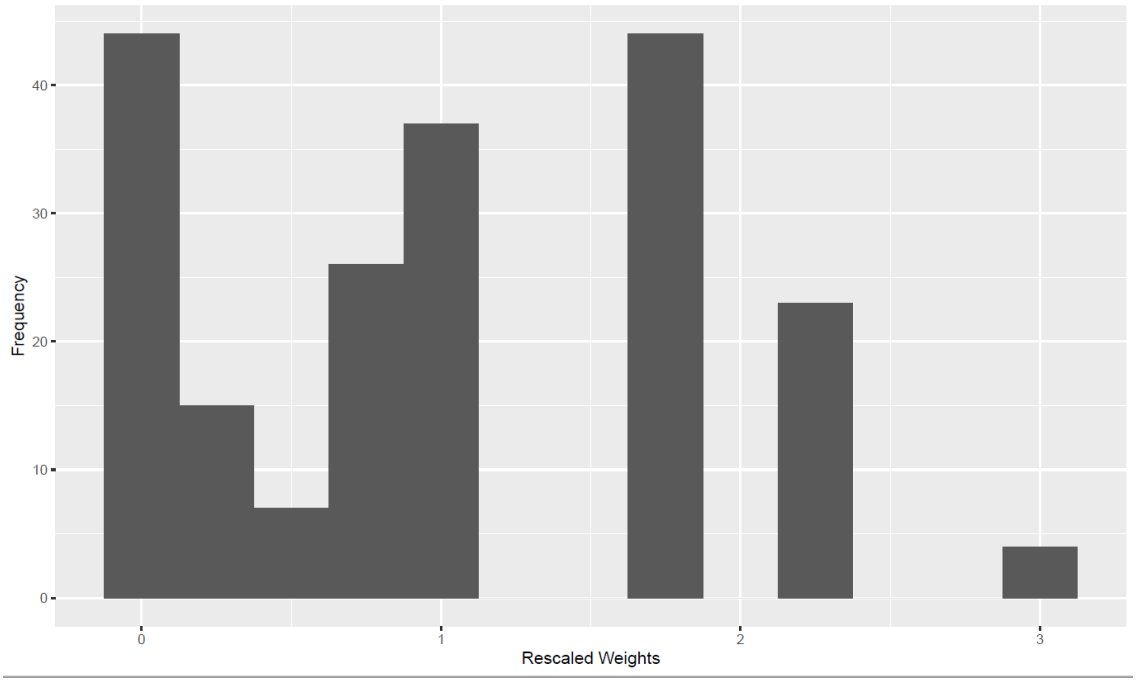


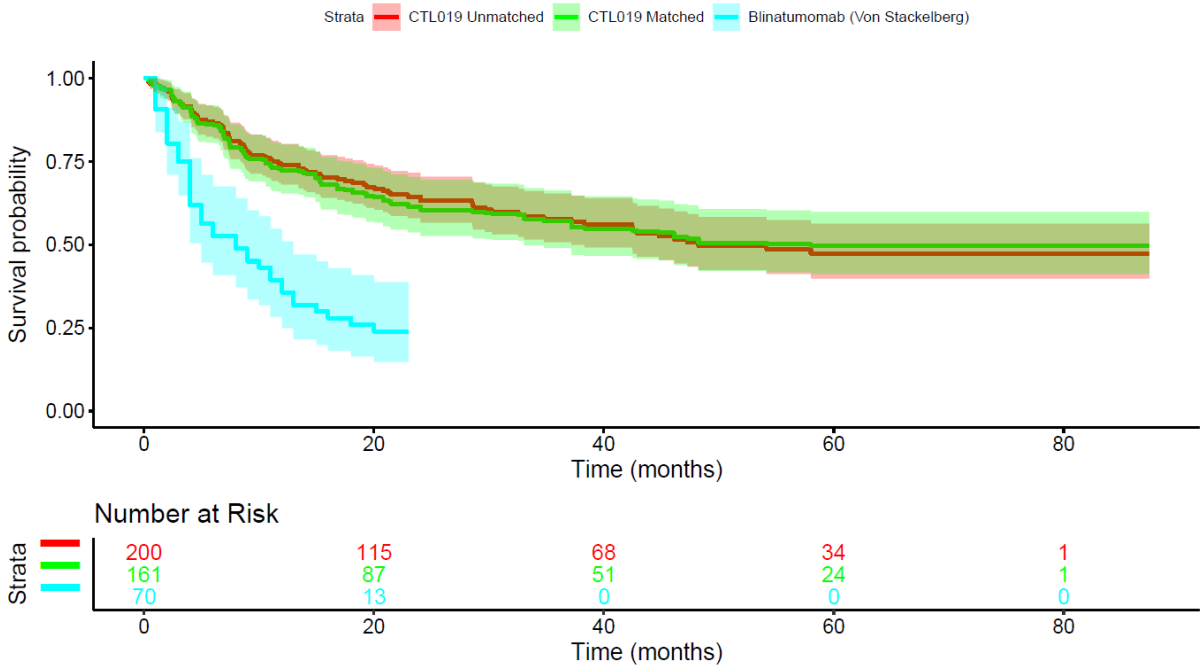
Figure 12: Distribution of weights of patients in the pooled tisagenlecleucel data in the comparison with Jeha *et al.* (2006) (reproduced from CS Appendix D, Figure 3)



The results of the MAIC analyses are reported for OS. EFS data from the comparator studies were not available. The unmatched tisagenlecleucel Kaplan-Meier curve, the matched tisagenlecleucel Kaplan-Meier curve and the blinatumomab Kaplan-Meier curve are presented in Figure 13. Both the unmatched and matched tisagenlecleucel curves are higher than the blinatumomab curve, but the unmatched and

matched tisagenlecleucel curves are quite close to each other, indicating that the adjustments of the two included covariates – previous remissions/relapses and prior HSCT – made little difference to the results.

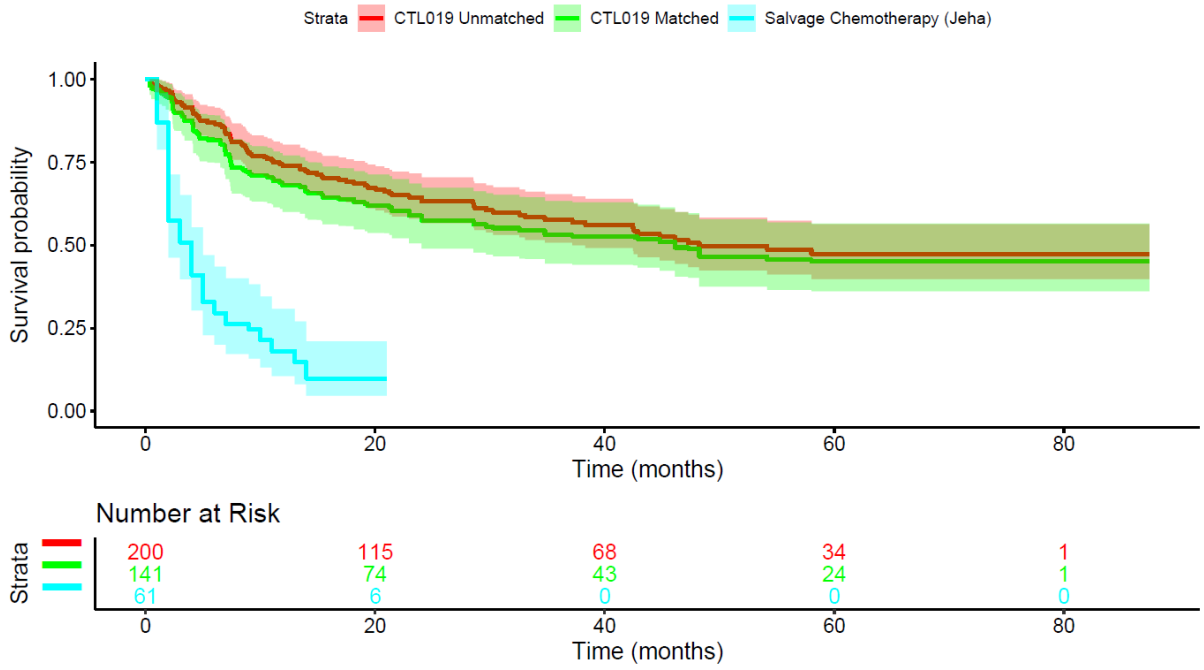
Figure 13: Overall survival for pooled tisagenlecleucel versus blinatumomab (reproduced from CS Appendix D, Figure 4)



Shaded regions represent 95% CIs.
CI - confidence interval; CTL019 - tisagenlecleucel
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] ENSIGN CSR (DCO: 24th May 2019);[35] B2101J CSR (DCO: 7th May 2018);[36] von Stackelberg et al. (2016).[15]

The unmatched tisagenlecleucel Kaplan-Meier curve, the matched tisagenlecleucel Kaplan-Meier curve and the salvage chemotherapy Kaplan-Meier curve are presented in Figure 14. Both the unmatched and matched tisagenlecleucel curves are higher than the salvage chemotherapy curve. The matched tisagenlecleucel curve is slightly lower than the unmatched tisagenlecleucel curve, indicating that tisagenlecleucel may work better for the unmatched population than the matched population.

Figure 14: Overall survival for pooled tisagenlecleucel versus salvage chemotherapy (reproduced from CS Appendix D, Figure 5)



Shaded regions represent 95% CIs.
CI - confidence interval; CTL019 - tisagenlecleucel
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] ENSIGN CSR (DCO: 24th May 2019);[35] B2101J CSR (DCO: 7th May 2018);[36] Jeha et al. (2016).[14]

Hazard ratios (HRs) from the MAIC analyses and the naïve comparisons are presented in Table 24. For tisagenlecleucel vs blinatumomab, the HR from the MAIC analysis is 0.32 (95% confidence interval [CI]: 0.21, 0.48) and the HR from the naïve comparison is 0.29 (95% CI: 0.20, 0.44). For tisagenlecleucel vs salvage chemotherapy, the HR from the MAIC analysis is 0.20 (95% CI: 0.14, 0.31) and the HR from the naïve comparison is 0.16 (95% CI: 0.11, 0.23). The point estimates from the MAIC results are slightly higher than those from the naïve ITCs for both comparators but the 95% CIs overlap to a large extent. The ESS for the two comparisons are 140.23 and 122.64 respectively, and the sample size in the pooled dataset is 200.

Table 24: Overall survival results based on the pooled data (reproduced from CS Appendix D, Table 21)

Adjustment scenario	Naïve comparison		MAIC		
	HR (95% CI)	*p*-value	ESS	HR (95% CI)	*p*-value
Tisagenlecleucel vs blinatumomab	0.29 (0.20, 0.44)	*p*<0.001	140.23	0.32 (0.21, 0.48)	*p*<0.001
Tisagenlecleucel vs salvage chemotherapy	0.16 (0.11, 0.23)	*p*<0.001	122.64	0.20 (0.14, 0.31)	*p*<0.001

CI - confidence interval; ESS - effective sample size; HR - hazard ratio; MAIC - matching-adjusted indirect comparison.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] ENSIGN CSR (DCO: 24th May 2019);[35] B2101J CSR (DCO: 7th May 2018);[36] von Stackelberg et al. (2016).[15]

4.9.3 ITC using ELIANA only

The company also conducted a MAIC analysis with data on tisagenlecleucel from the ELIANA study only.[34] Similar to the MAIC analysis with pooled data, covariates that are potential effect modifiers were considered and their importance for adjustment provided by the company is listed in Table 21. The company selected the effect modifiers of high importance to be included in the MAIC based on data availability and input from clinical experts, as well as making sure that the ESS was at least 50% of the patient population.

In the comparison against blinatumomab, a total of six covariates were considered in the analyses, including trisomy 21, previous remissions/relapses, prior HSCT, BCR-ABL, hypodiploidy, blast count. After adjustment, the mean of the six included covariates is balanced between the adjusted tisagenlecleucel population and the von Stackelberg population, as shown in Table 25. Differences still exist in the unadjusted covariates: MLL total (3.64% vs 14.29%), months since last relapse (3.68 vs 2.90), age (11.30 vs 8.00) and sex (male, 57.12% vs 67.14%).

In the comparison against salvage chemotherapy, only three covariates were adjusted for, including prior HSCT, number of prior lines of therapy, and BCR-ABL. After adjustment, the mean of the three included covariates is balanced between the adjusted tisagenlecleucel population and the Jeha *et al.* population, as shown in Table 26. Differences still exist in the unadjusted covariates: hypodiploidy (0.07% vs 9.84%), age (12.75 vs 12.00) and sex (male, 56.43% vs 60.66%). It is unclear whether trisomy 21 (high importance for adjustment), months since last relapse, previous remissions/relapses, MLL total, and blast count are balanced as these covariates are not reported in the Jeha *et al.* study.[14]

Table 25: Summary of baseline characteristics of ELIANA and von Stackelberg *et al.* (2016) before and after adjustment (reproduced from CS, Table 24)

Characteristic	Adjusted for?	ELIANA		Comparator
		Before adjustment	After adjustment	von Stackelberg *et al.* (2016)
Trisomy 21 (%)	Yes	7.59	2.86	2.86
Previous remissions/relapses = 0 (%)	Yes	7.59	2.86	2.86
Previous remissions/relapses = 1 (%)	Yes	26.58	44.29	44.29
Previous remissions/relapses = 2 (%)	Yes	21.52	41.43	41.43
Previous remissions/relapses = 3+ (%)	Yes	44.30	11.43	11.43
Prior HSCT (%)	Yes	60.76	57.14	57.14
Number of prior lines of therapy (mean)	No	3.45	3.02	NR
MLL total (%)	No	1.27	3.64	14.29
BCR-ABL (%)	Yes	2.53	2.86	2.86
Months since last relapse (mean)	No	4.25	3.68	2.90
Hypodiploidy (%)	Yes	1.27	5.71	5.71
Blast count (%)	Yes	68.35	74.29	74.29
Age (mean)	No	12.04	11.30	8.00
Sex, male (%)	No	56.96	57.12	67.14

BCR-ABL - breakpoint cluster region-Abelson; HSCT - haematopoietic stem cell transplant; MLL - mixed-lineage leukaemia; NR - not reported.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] von Stackelberg et al. (2016).[15]

Table 26: Summary of baseline characteristics of ELIANA and Jeha *et al.* (2006) before and after adjustment (reproduced from CS, Table 25)

Characteristic	Adjusted for?	ELIANA		Comparator
		Before adjustment	After adjustment	Jeha *et al.* (2006)
Trisomy 21 (%)	No	7.59	10.67	NR
Previous remissions/relapses (mean)	No	2.35	1.88	NR
Prior HSCT (%)	Yes	60.76	29.51	29.51
Number of prior lines of therapy = 1 (%)	No	5.06	0.00	0.00
Number of prior lines of therapy = 2 (%)	Yes	27.85	37.70	37.70
Number of prior lines of therapy = 3 (%)	Yes	25.32	36.07	36.07
Number of prior lines of therapy = 4 (%)	Yes	18.99	21.31	21.31
Number of prior lines of therapy = 5 (%)	Yes	7.59	1.64	1.64
Number of prior lines of therapy = 6 (%)	Yes	15.19	3.28	3.28
MLL total (%)	No	1.27	1.42	NR
BCR-ABL (%)	Yes	2.53	4.92	4.92
Months since last relapse (mean)	No	4.25	4.06	NR
Hypodiploidy (%)	No	1.27	0.07	9.84
Blast count (%)	No	68.35	68.43	NR
Age (mean)	No	12.04	12.75	12.00
Sex, male (%)	No	56.96	56.43	60.66

BCR-ABL - breakpoint cluster region-Abelson; HSCT - haematopoietic stem cell transplant; MLL - mixed-lineage leukaemia; NR - not reported.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] Jeha et al. (2006).[14]

Histogram plots of rescaled weights for the comparisons with von Stackelberg *et al.*[15] and Jeha *et al.*[14] are presented in Figure 15 and Figure 16, respectively. Overall, the majority of the weights are between 0 and 2. In the comparison with von Stackelberg *et al.*, the largest weight is around 4.5, and in the

comparison with Jeha *et al*., the largest weight is close to 3. ELIANA[34] included 79 patients at baseline: more than 35 (44%) patients have weights close to 0 in the comparison with von Stackelberg *et al.*, and more than 25 (32%) patients have weights close or equal to 0 in the comparison with Jeha *et al*.

Figure 15: Distribution of weights of patients in ELIANA in the comparison with von Stackelberg *et al.* (2016) (reproduced from CS, Figure 22)

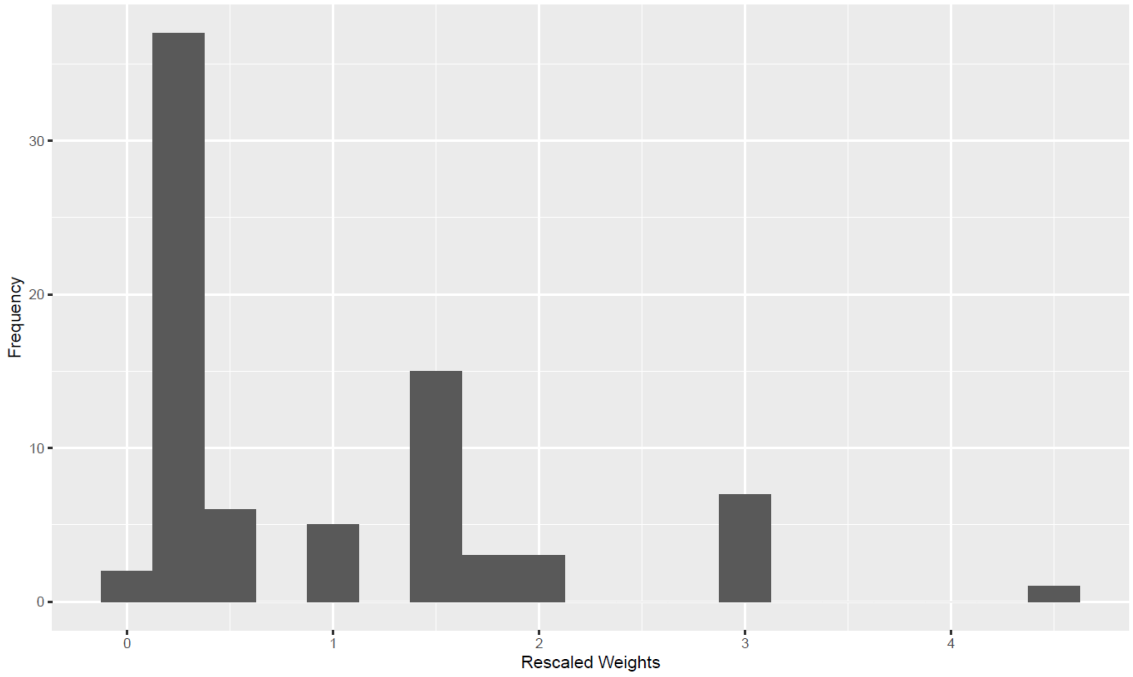
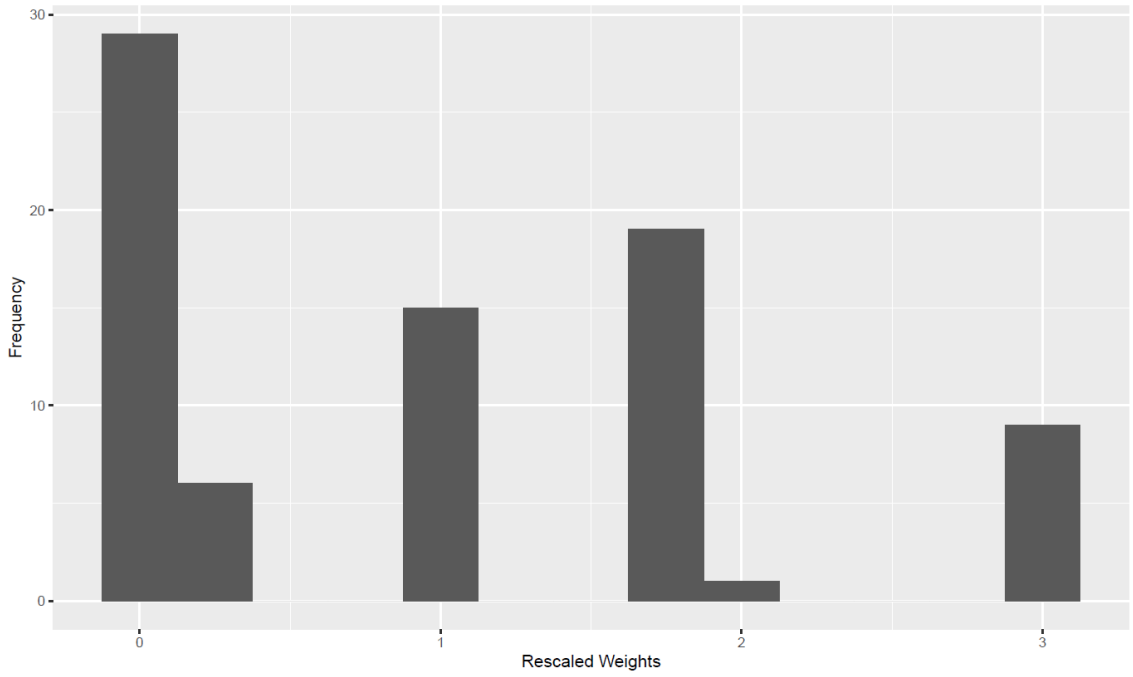
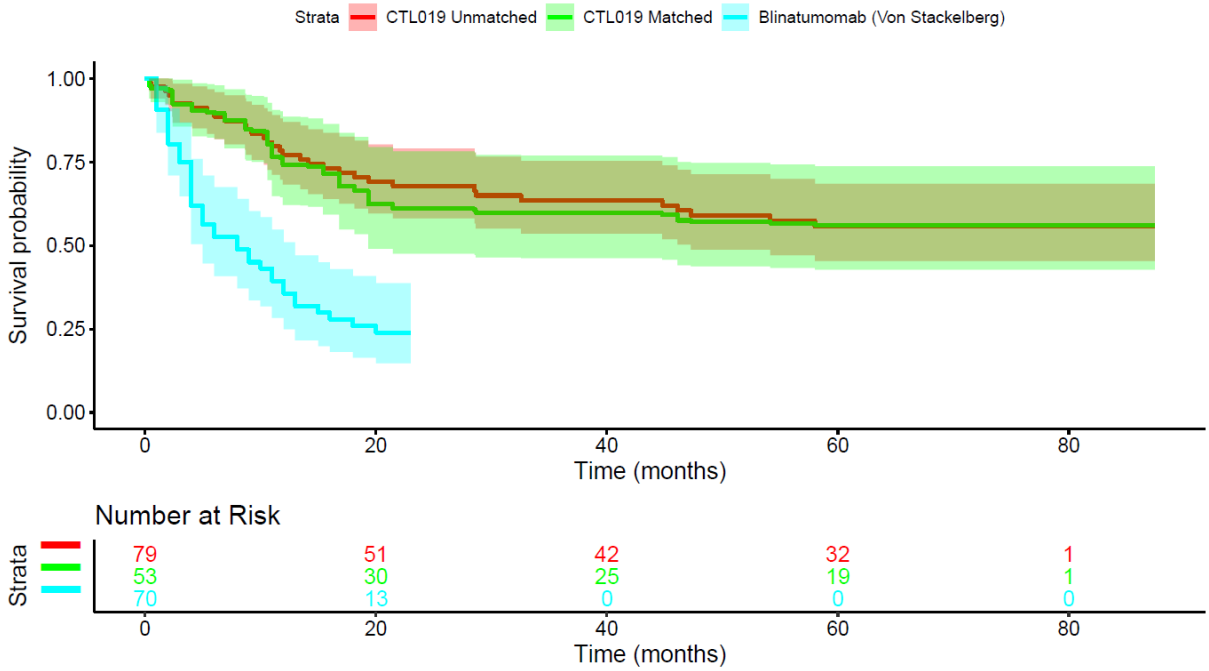


Figure 16: Distribution of weights of patients in ELIANA in the comparison with Jeha *et al.* (2006) (reproduced from CS, Figure 23)



The results of the MAIC analyses are reported for OS. EFS data are not available for the comparators. The unmatched tisagenlecleucel Kaplan-Meier curve, the matched tisagenlecleucel Kaplan-Meier curve and the blinatumomab Kaplan-Meier curve are presented in Figure 17. The unmatched and matched tisagenlecleucel curves are higher than the blinatumomab curve and the matched tisagenlecleucel curve is slightly lower than the unmatched tisagenlecleucel curve.

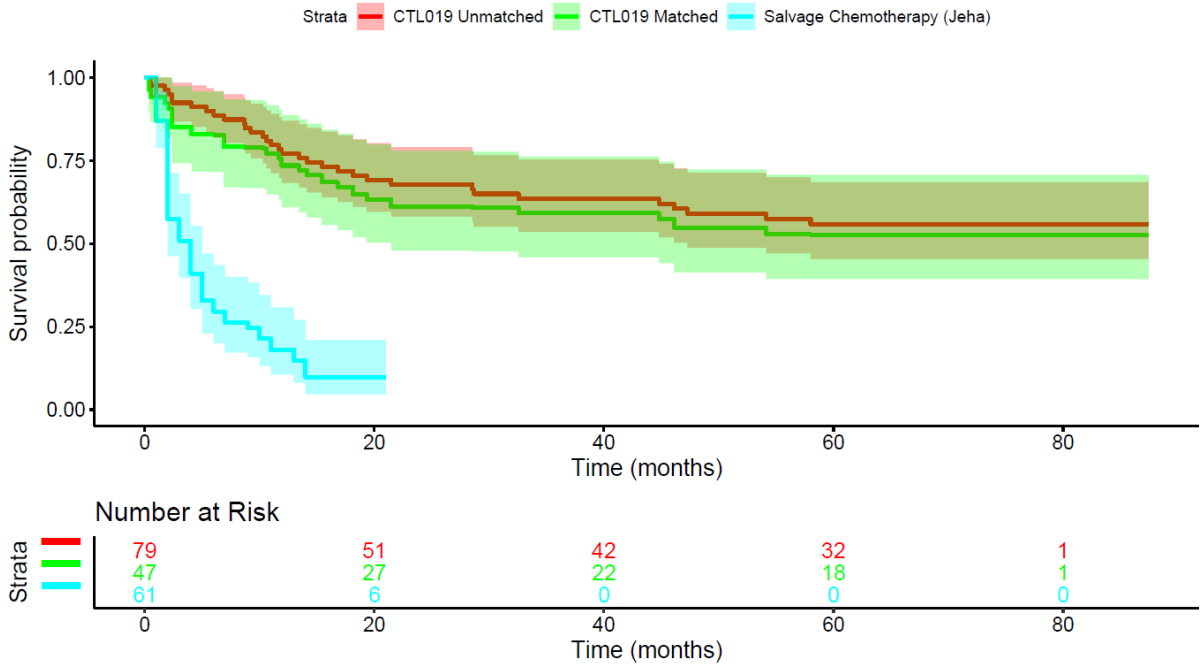
Figure 17: Overall survival for ELIANA tisagenlecleucel versus blinatumomab (reproduced from CS, Figure 24)



Shaded regions represent 95% CIs.
Abbreviations: CI - confidence interval; CTL019 - tisagenlecleucel
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] von Stackelberg et al. (2016).[15]

The unmatched tisagenlecleucel Kaplan-Meier curve, the matched tisagenlecleucel Kaplan-Meier curve and the salvage chemotherapy Kaplan-Meier curve are presented in Figure 18. Both the unmatched and matched tisagenlecleucel curves are higher than the salvage chemotherapy curve. The matched tisagenlecleucel Kaplan-Meier curve is slightly lower than the unmatched tisagenlecleucel curve, indicating that tisagenlecleucel may work better for the unmatched population than the matched population.

Figure 18: Overall survival for ELIANA tisagenlecleucel versus salvage chemotherapy (reproduced from CS, Figure 25)



Shaded regions represent 95% CIs.
Abbreviations: CI - confidence interval; CTL019 - tisagenlecleucel
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] Jeha et al. (2006).[14]

HRs from the MAIC analyses and the naïve comparisons are presented in Table 27. For tisagenlecleucel vs blinatumomab, the HR from the MAIC analysis is 0.31 (95% CI: 0.18, 0.55) and the HR from the naïve comparison is 0.26 (95% CI: 0.16, 0.43). For tisagenlecleucel vs salvage chemotherapy, the HR from the MAIC analysis is 0.19 (95% CI: 0.10, 0.35) and the HR from the naïve comparison is 0.14 (95% CI: 0.09, 0.24). The point estimates from the MAIC results are slightly higher than the results from the naïve comparisons for both comparators but the 95% CIs overlap to a large extent. The ESS for the two comparisons are 41.60 and 41.34 respectively, and the sample size in the ELIANA study is 79.[34]

Table 27: Overall survival results based on ELIANA alone (reproduced from CS, Table 26)

Adjustment scenario	Naïve comparison		MAIC		
	HR (95% CI)	*p*-value	ESS	HR (95% CI)	*p*-value
Tisagenlecleucel vs blinatumomab	0.26 (0.16, 0.43)	*p*<0.001	41.60	0.31 (0.18, 0.55)	*p*<0.001
Tisagenlecleucel vs salvage chemotherapy	0.14 (0.09, 0.24)	*p*<0.001	41.34	0.19 (0.10, 0.35)	*p*<0.001

CI - confidence interval; ESS - effective sample size; HR - hazard ratio; MAIC - matching-adjusted indirect comparison.
Sources: ELIANA CSR (DCO: 17th Nov 2022);[34] von Stackelberg et al. (2016);[15] Jeha et al. (2006).[14]

4.10 Indirect treatment comparison: Critique of statistical methods

The EAG has concerns regarding the MAIC analyses conducted by the company. The differences in baseline characteristics between the tisagenlecleucel and comparator studies have not been properly adjusted for. The company only considered potential treatment effect modifiers of high importance in the matching to achieve a balance between clinical relevance and sufficient ESS. For an unanchored indirect comparison where the common comparator is unavailable, all effect modifiers and prognostic variables should be adjusted for, in order to reliably predict absolute outcomes. The likely extent of error due to unaccounted for covariates is unknown.[61] In addition, for the potential effect modifiers that are included in the analysis, the company has selected different covariates for the same comparison without sufficient justification. In the comparison against blinatumomab, two covariates were adjusted for when using the pooled tisagenlecleucel data, but six covariates were included in the analysis using ELIANA only.[34] In the comparison against salvage chemotherapy, two covariates were adjusted for when using the pooled tisagenlecleucel data, but three covariates were included in the analysis using ELIANA study. For the potential effect modifiers of high importance that are not reported in the von Stackelberg *et al.* and Jeha *et al.* studies,[14, 15] the residual bias due to unobserved prognostic factors and effect modifiers has not been quantified.

The target population of the MAIC analyses has not been clearly stated. It is unclear how similar the matched tisagenlecleucel population is to the aggregate comparator population and whether the derived relative treatment effect is applicable to the target population for this appraisal. The EAG considers that the MAIC results should be interpreted with caution.

The company's economic model (described in Section 5.2) uses naïve ITCs based on the unadjusted ELIANA data, given the lack of meaningful differences between the unadjusted and adjusted HRs. The results of the naïve ITCs should also be interpreted with caution as the between-study differences have not been adjusted for. However, it should also be noted that including the MAIC-adjusted OS in the economic model has virtually no impact on the ICER (see Table 55). The EAG prefers the use of pooled tisagenlecleucel data over the use of ELIANA study alone as the pooled dataset has a larger sample size than the ELIANA study and the baseline characteristics of the pooled dataset are considered generally representative of the population of patients treated with tisagenlecleucel in the NHS.

4.11 Conclusions of the clinical effectiveness section

Effectiveness and safety of tisagenlecleucel: The CS[9] presents data on three single-arm studies of tisagenlecleucel (ELIANA,[34] ENSIGN[35] and B2101J[36]) in a total of 200 patients aged up to 25 years with B-cell ALL that is refractory, in relapse post-SCT, in second or later relapse, or ineligible for SCT. In addition, the NHSE SACT dataset[37] provides data on 121 patients receiving tisagenlecleucel in England during the managed access period. Across the three pooled clinical studies, 57% had prior SCT

(the proportion with prior SCT was unclear for the NHSE dataset). The proportion receiving subsequent allo-SCT was 23% in ELIANA, 14% in ENSIGN and 14% in B2101J (18% pooled across studies), while the proportion in the NHSE dataset was reported as 11% (though the EAG questioned the reliability of this estimate). Median EFS was 21 months across the three pooled clinical studies. Median OS was 48 months across the three pooled studies, while in the NHSE dataset, median OS was not reached (3-year OS was 67%). For patients enrolled but not successfully infused with tisagenlecleucel, median OS was 1.9 months in ELIANA, 1.5 months in ENSIGN and not estimable in B2101J. Frequent AEs included CRS (81%), hypogammaglobulinaemia (51%) and decreases in white blood cells (57%), neutrophils (52%) and platelets (47%). Deaths potentially related to tisagenlecleucel occurred in 3/79 (3.8%) patients in ELIANA (intracranial haemorrhage, systemic mycosis and viral encephalitis) while none were reported in ENSIGN or B2101J. The EAG's main concerns regarding the clinical data are:

- Clinical advisors to the EAG raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from more stringent definitions of EFS. ELIANA-defined EFS does not consider MRD positivity or loss of B-cell aplasia as events and includes censoring for allo-SCT and further therapy. This approach may exaggerate the absolute benefits of tisagenlecleucel if subsequent allo-SCT was due to MRD-positivity or loss of B-cell aplasia, as this may indicate that the treatment has failed but this failure would be masked by the censoring mechanism. In a UK real-world analysis of 128 patients,[45] median EFS was 22 months using the ELIANA definition or 7 months using a more stringent definition (including molecular relapse and further therapy as events).

ITCs: As the tisagenlecleucel studies were single-arm, the company conducted a MAIC for OS. The company preferred to include only the ELIANA[34] study for tisagenlecleucel, while the EAG considered that, given the similarities in design and populations, the pooled dataset including all three studies (N=200) should be used in the MAIC. The MAIC included two comparators: blinatumomab and salvage chemotherapy. For blinatumomab, the company used a single-arm study of 70 patients by von Stackelberg *et al.,* 2016[15] (subsequent allo-SCT rate 34%; median OS 7.5 months). For salvage chemotherapy, the company used a single-arm study of 61 patients by Jeha *et al.*, 2006[14] (subsequent allo-SCT rate 15%; median OS 3 months). The MAIC for tisagenlecleucel vs. blinatumomab gave an HR for OS of 0.32 (95% CI: 0.21 to 0.48; $p<0.001$), while the MAIC for tisagenlecleucel vs. salvage chemotherapy gave an HR for OS of 0.20 (95% CI: 0.14 to 0.31; $p<0.001$). The EAG's main concerns regarding the ITC are:

- The EAG considers that the company's selection of comparator studies was neither transparent nor well justified. The rates of subsequent allo-SCT and observed OS in both studies are lower than the rates expected by clinical experts consulted by the company and the EAG. Clinical advisors to the EAG indicated that lower SCT rates would likely lead to fewer patients achieving long-term survival. Whilst none of the studies identified in the company's SLR

perfectly align with the target population for tisagenlecleucel, the EAG's clinical advisors suggested that the RIALTO[47] study (subsequent allo-SCT rate 53%; median OS 14.6 months) may better reflect outcomes for patients receiving blinatumomab. For salvage chemotherapy, one of the EAG's clinical advisors suggested that the study by Kuhlen *et al*.[52] (subsequent allo-SCT rate 26%; median OS 6 months) may better reflect outcomes for FLAG-IDA, while another clinical advisor suggested that OS for FLAG-IDA may lie between the estimates reported by Jeha *et al.* and Kuhlen *et al.*

- The HRs for OS for tisagenlecleucel versus its comparators based on the MAIC are very similar to the HRs obtained from naïve ITCs. The EAG does not believe that all relevant prognostic factors and treatment effect modifiers have been included and properly adjusted for in the MAIC.

5 COST EFFECTIVENESS

5.1 Critique of the company's review of existing economic analyses

5.1.1 Summary of the company's review methods

The company undertook an SLR of existing cost-effectiveness studies to support the development of a cost-effectiveness model for tisagenlecleucel as a treatment for patients aged up to 25 with R/R B-cell ALL. The company's review was conducted according to a pre-defined protocol. Studies were eligible for inclusion in the review if they related to paediatric and young adult patients aged <25 years with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. Interventions included, but were not limited to, tisagenlecleucel or other CAR-T cell therapies, blinatumomab, other anticancer therapies including chemotherapy, and allogeneic or autologous SCT. Only studies which were prioritised for data extraction were included in the review; in particular, studies which reported economic analyses reflecting a non-European study setting were de-prioritised. Included studies were critically appraised using the Drummond checklist.[62]

CS Appendix G[39] reports the company's searches for the review of existing economic evaluations studies, HRQoL studies and health care cost and resource use studies. These searches were run simultaneously on 20th March 2023, though the reviews themselves are reported in Appendices G, H and I, respectively. Searches covered all key databases (MEDLINE including Medline-in-Process and Epub ahead of print; Embase; the Health Technology Assessment (HTA) database via INAHTA, and the NHS Economic Evaluation Database as archived by CRD); the Tufts Cost-Effectiveness Analysis (CEA) registry; and the last two years of proceedings from congresses including ASCO, ESMO and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The websites of a selection of international HTA bodies were also checked for relevant HTAs published since 2019. Reference lists of relevant review articles or HTA documents were checked for missed studies.

5.1.2 Summary and critique of company's review of existing economic evaluations

The company's review identified 16 economic analyses published across 17 publications/reports. Of these, the company prioritised eight unique economic evaluations for data extraction; these studies are summarised in Table 28.

Six of the eight included studies were model-based economic evaluations of tisagenlecleucel. Across these six economic analyses, the comparators included blinatumomab, FLAG-IDA, clofarabine monotherapy and/or clofarabine combination therapy (clofarabine, etoposide and cyclophosphamide [CEC]). Two studies[63, 64] did not include tisagenlecleucel – these were evaluations of blinatumomab and clofarabine combination therapy. The six economic analyses of tisagenlecleucel reflected various European health care settings including Ireland, the Netherlands, Spain, Scotland, Switzerland and Norway. Four of the six tisagenlecleucel studies were available as full text publications,[65-68] whilst the

remaining two reports[69, 70] were HTA agency guidance documents. All six of the tisagenlecleucel analyses described the use of a partitioned survival model, with some of the publications/reports also mentioning the use of a linked decision tree to account for pre-treatment costs and health outcomes for patients in whom tisagenlecleucel infusion was planned but not administered.

The EAG notes the following with respect to the company's review:

- Overall, the searches appear to have been well-designed and executed. Where filters were used to identify each of the study types eligible for inclusion, these were based on the work of the Scottish Intercollegiate Guidelines Network (SIGN); while these filters are not always validated (as is implied on page 83 of the CS appendices), they are acknowledged as being from a credible source and are widely used in STA submissions of this type. The EAG considers that the searches are likely to have been sufficient to find all eligible evidence for inclusion in the reviews of economic evaluations, HRQoL and resource use and costs.
- All six economic analyses of tisagenlecleucel used a partitioned survival model.
- All of the included economic analyses of tisagenlecleucel included a 5-year cure assumption whereby after this timepoint mortality risk was based on general population life tables uplifted using a standardised mortality ratio (SMR) of 9.05 or higher (note: the Scottish Medicines Consortium [SMC] technical briefing for tisagenlecleucel[69] does not report the value of the SMR used in the base case or sensitivity analyses).
- All of the included economic analyses of tisagenlecleucel were informed by pooled clinical outcomes data from ELIANA and ENSIGN.[34, 35] Five of the six tisagenlecleucel studies also included B2101J[36] within the pooled tisagenlecleucel dataset.
- Some of the economic analyses were informed by MAICs, whilst others were informed by naïve ITCs.
- The previous appraisal of tisagenlecleucel for the treatment of R/R ALL (NICE TA554[19]) was not included in the company's review. The EAG is unclear why this is the case, as this appraisal met the inclusion criteria for the company's review and should have met the conditions for being prioritised for data extraction.
- Amongst the economic analyses which did not include tisagenlecleucel, the company included the French Haute Autorité de Santé (HAS) evaluation of blinatumomab for adults with R/R Ph-negative ALL.[63] It is unclear why other relevant evaluations of blinatumomab for this same indication (e.g., NICE TA450[21] and SMC Advice ID 1145/16[71]) were not included in the review. Again, the economic analyses undertaken to inform these appraisals met the inclusion criteria for the company's review and should have met the conditions for being prioritised for data extraction.

Table 28: Summary of existing economic analyses included in the company's review

Study	Publication type	Country	Population	Interventions/ comparators	Model type	Tisagenlecleucel data sources	Cure assumptions	ITC methods
Included economic analyses of tisagenlecleucel								
Carey *et al.* (2022)[65]	Full text publication	Ireland	Paediatric and young adults with R/R ALL	• Tisagenlecleucel • Blinatumomab	Decision tree plus PartSA	Pooled dataset (ELIANA and ENSIGN)	Cure point at 5 years, SMR=15.5	Naïve ITC
Moradi-Lakeh *et al.* (2021)[67]	Full text publication	Switzerland	R/R paediatric ALL	• Tisagenlecleucel • CEC • Blinatumomab	PartSA	Pooled dataset (ELIANA, ENSIGN and B2101J)	Cure point at 5 years, SMR=9.05	MAIC
Thielen *et al.* (2020)[68]	Full text publication	Netherlands	Paediatric patients with R/R ALL	• Tisagenlecleucel • C-mono • CEC	PartSA	Pooled dataset (ELIANA, ENSIGN and B2101J)	Cure point at 5 years, SMR=15.2	Appears to be naïve ITC
Ribera Santasusana *et al.* (2020)[66]	Full text publication	Spain	Paediatric and young adult patients with R/R ALL	• Tisagenlecleucel • FLAG-IDA	PartSA	Pooled dataset (ELIANA, ENSIGN and B2101J)	Cure point at 5 years, SMR=9.05	Appears to be naïve ITC
SMC (2019)[69]	Guidance document	Scotland	Paediatric and young adult patients with R/R ALL	• Tisagenlecleucel • Blinatumomab • FLAG-IDA	Decision tree plus PartSA	Pooled dataset (ELIANA, ENSIGN and B2101J)	Cure point at 5 years, SMR not reported	Naïve ITC. MAIC included in sensitivity analysis.
NoMA (2018)[70]	Guidance document	Norway	Paediatric and young adult patients with R/R ALL	• Tisagenlecleucel • CEC	PartSA	Pooled dataset (ELIANA, ENSIGN and B2101J)	Cure point at 5 years, SMR=9.05	MAIC and naïve ITCs included.
Included economic analyses which do not include tisagenlecleucel								
HAS (2022)[63]	Guidance document	France	Adults with B-precursor R/R ALL, Philadelphia-negative	• Blinatumomab • Standard chemo	No details of model provided	N/a	No details of model provided	N/a
Lis *et al.* (2012)[64]	Full text publication	Poland	Paediatric and young adult patients with R/R ALL after ≥2 previous standard treatments	• CEC • Nelarabine • FLAG-IDA	Decision tree	N/a	Not reported	N/a

ITC - indirect treatment comparison; R/R - relapsed/refractory; ALL - acute lymphoblastic leukaemia; MAIC - matching-adjusted indirect comparison; PartSA - partitioned survival model; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; CEC - clofarabine, etoposide and cyclophosphamide; C-mono - clofarabine monotherapy; NoMA - Norwegian Medicines Agency; HAS - Haute Autorité de Santé; N/a - not applicable

5.2 Description of the company's original economic analysis

This section describes the company's original submitted economic model, as described in the CS.[9] As part of their clarification response, the company provided two updated versions of the economic model which include some minor error corrections and additional functionality. The latest version of the revised model is discussed separately in Section 5.4.

5.2.1 Scope of the company's economic analysis

As part of their submission to NICE,[9] the company submitted an executable health economic model programmed in Microsoft Excel.® The scope of the company's economic analysis is summarised in Table 29.

Table 29: Scope of the company's economic analysis

Population	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse
Time horizon	88 years (lifetime)
Intervention	Tisagenlecleucel (administered as a single dose by IV infusion)
Comparators	(i) Blinatumomab (ii) FLAG-IDA
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2021/22 (except for drug costs which reflect current prices)

ALL - acute lymphoblastic leukaemia; IV - intravenous; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

The company's model assesses the cost-effectiveness of tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA for the treatment of paediatric and young adult patients with R/R B-cell ALL. Cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of NHS and Personal Social Services (PSS) over an 88-year (lifetime) horizon. Unit costs are valued at 2021/22 prices, except for drug acquisition costs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The company's economic analysis reflects the patient population enrolled in the ELIANA study.[34] This population relates to paediatric and young adult patients (aged up to 25 years) with B-cell ALL which is refractory, in relapse post-transplant, or in second or later relapse. The patient population is in line with the full marketing authorisation for tisagenlecleucel in R/R B-cell ALL.[28] At model entry, patients are assumed to be 12 years of age and 43% of the population is assumed to be female. The modelled population reflects patients in whom tisagenlecleucel infusion is planned, which includes patients who receive the infusion as well as patients who do not receive the infusion.

Intervention

The intervention included in the company's economic analysis is tisagenlecleucel, which is administered as a once-only treatment via IV infusion. The assumed dosing of tisagenlecleucel is consistent with the dose administered in the ELIANA study: 0.2 to 5.0×10^6 tisagenlecleucel cells per kg body weight (for patients $\leqslant$50 kg), or 0.1 to 2.5×10^8 tisagenlecleucel cells (non-weight based) (for patients >50 kg). Prior to receiving the infusion with tisagenlecleucel, patients are assumed to receive pre-treatment procedures and drugs (leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy). Further details regarding the chemotherapy regimens which comprise pre-treatment for tisagenlecleucel are provided in Section 5.2.4 (Table 43).

Comparators

Section B.3.2.3 of the CS[9] states that there is no established treatment for patients with R/R B-cell ALL, and that until the introduction of tisagenlecleucel, the disease has been managed on a case-by-case basis, taking into account patient fitness, treatment goals, response and durability of response to prior therapy.

The company's economic analysis includes two comparators: (i) blinatumomab and (ii) salvage chemotherapy, which is assumed to be FLAG-IDA. OS outcomes for blinatumomab and FLAG-IDA are informed by single-arm studies reported by von Stackelberg *et al*.[15] and Jeha *et al*.,[14] respectively. These comparators and data sources are the same as those applied in the company's model in TA554.[19]

The dosing schedule for blinatumomab for patients aged up to 18 years in the model was derived from von Stackelberg *et al.*[15] Adjusted dosing for adults was assumed for patients aged over 18 years (see Section 5.2.4, Table 43). Patients are assumed to receive up to two cycles of treatment with blinatumomab.

The CS[9] states that based on feedback obtained from UK clinical experts, the salvage chemotherapy regimen of choice would be FLAG-IDA. However, the CS highlights that there are no suitable effectiveness data for FLAG-IDA, and so data on clofarabine monotherapy were used as a proxy. FLAG-IDA is assumed to be administered in a single cycle.

Allo-SCT is not included as a comparator in the model. However, the model assumes that a proportion of patients who receive tisagenlecleucel, blinatumomab or FLAG-IDA may go on to receive subsequent allo-SCT. No other active or palliative treatments are included in the model.

Other comparators listed in the NICE scope[29] – inotuzumab ozogamicin, TKIs and BSC – are not included in the model.

5.2.2 Model structure and logic

The company's model uses a hybrid approach which includes an initial decision tree for patients for whom the tisagenlecleucel infusion is planned (see Figure 19), and a partitioned survival model which estimates lifetime health outcomes and costs for the intervention and comparator groups based on the treatment received (see Figure 20). The decision tree is applied only to patients in the tisagenlecleucel group. Patients in the tisagenlecleucel group who do not receive tisagenlecleucel (either due to AEs or manufacturing error) are assigned costs associated with pre-treatment chemotherapy and outcomes and costs associated with the comparators. Patients in the tisagenlecleucel group who die prior to receiving the infusion are assumed to incur some pre-treatment costs and accrue zero life years and zero QALYs. The partitioned survival component of the model applies to all three treatment groups and is comprised of three mutually exclusive and jointly exhaustive health states: (i) event-free (EF), (ii) relapsed/progressed disease (PD), and (iii) dead (see Figure 20).

Figure 19: Company's decision tree structure for patients in whom treatment with tisagenlecleucel is planned

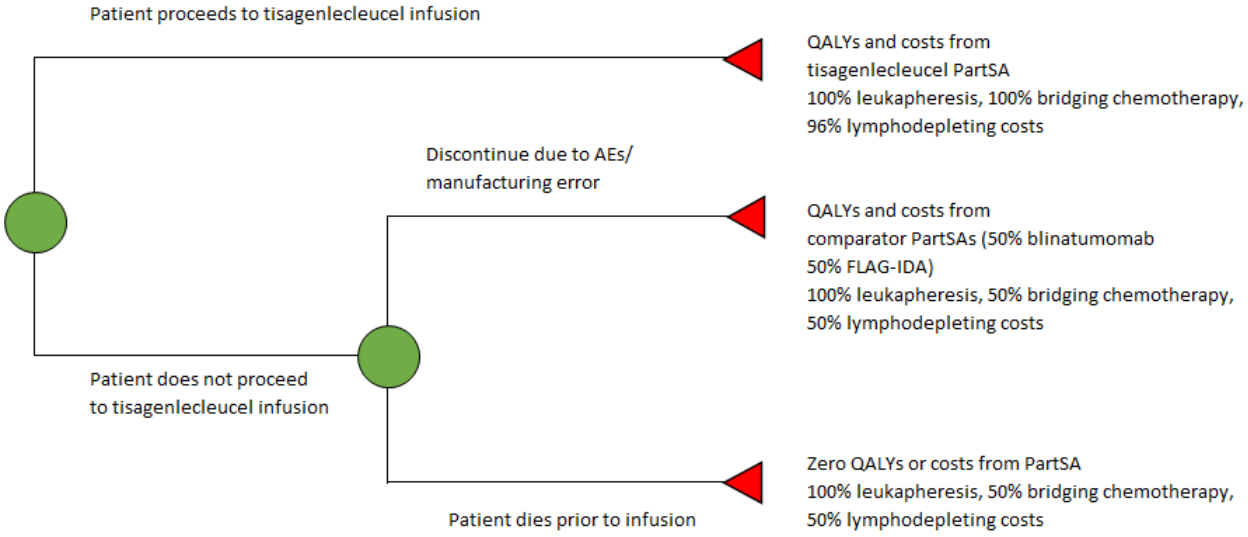
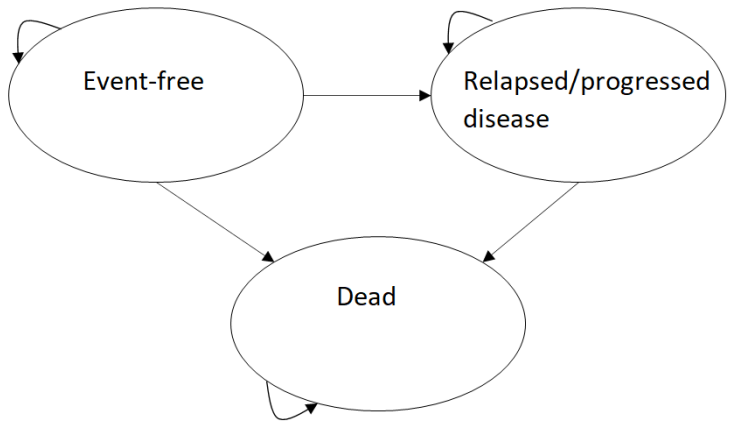


Figure 20: Company's partitioned survival model for treatments received



Decision tree model for patients in whom tisagenlecleucel infusion is planned

The decision tree component of the company's model (Figure 19) is intended to account for differences in outcomes and costs for patients who receive the tisagenlecleucel infusion and for those who do not proceed to infusion. Potential reasons for non-infusion of tisagenlecleucel include: (i) failures in the tisagenlecleucel manufacturing process; (ii) AEs leading to the patient being considered ineligible for tisagenlecleucel infusion or (iii) patient death prior to infusion. The decision tree includes the following assumptions:

- 81.4% of patients go on to receive the tisagenlecleucel infusion. These patients subsequently enter into the partitioned survival model. 100% of these patients are assumed to incur of the costs of leukapheresis and bridging chemotherapy and 96% incur the cost of lymphodepleting chemotherapy.
- 11.3% of patients do not receive the tisagenlecleucel infusion due to manufacturing failure or AEs. In these cases, the model assumes that 50% of patients subsequently receive blinatumomab and 50% receive FLAG-IDA; lifetime health outcomes and costs for these patients are drawn from the partitioned survival models for the blinatumomab and FLAG-IDA groups. 100% of these patients are assumed to incur the cost of leukapheresis and 50% incur the costs of bridging chemotherapy and lymphodepleting chemotherapy.
- 7.2% of patients die before receiving the tisagenlecleucel infusion. These patients are assumed to accrue zero life years, zero QALYs and zero treatment costs. 100% of these patients are assumed to incur the costs of leukapheresis and 50% incur the costs of bridging chemotherapy and lymphodepleting chemotherapy.

Partitioned survival model for all treatment groups

The partitioned survival model (Figure 20) operates as follows. Patients with R/R B-cell ALL enter the model in the EF state and receive treatment with either tisagenlecleucel (following the pre-treatments described above) or a comparator treatment (blinatumomab or FLAG-IDA). After initial treatment with tisagenlecleucel, blinatumomab or FLAG-IDA, a proportion of patients undergo subsequent allo-SCT; the proportions of patients proceeding to SCT differs between the treatment groups (tisagenlecleucel allo-SCT rate = 22.78%; blinatumomab allo-SCT rate = 34.29%; FLAG-IDA allo-SCT rate = 14.75%).[14, 15, 34] With the exception of allo-SCT, the model assumes that patients do not receive any other subsequent active cancer treatments following relapse/progression. At any time *t,* health state occupancy is determined by the cumulative probabilities of OS and EFS, whereby: the probability of being alive and event-free is given by the cumulative probability of EFS; the probability of being alive following disease relapse/progression is determined by the cumulative probability of OS minus the cumulative probability of EFS, and the probability of being dead is estimated as one minus the cumulative probability of OS. Patients are redistributed across the three health states at the end of each monthly cycle. The model includes a half-cycle correction.

The cumulative probabilities of OS and EFS for patients receiving tisagenlecleucel are modelled using mixture-cure models (MCMs) fitted to the time-to-event data from ELIANA[34] (DCO: Nov 2022). The same approach is used for both blinatumomab and FLAG-IDA using MCMs fitted to replicated individual patient data (IPD) on OS from von Stackelberg *et al*.[15] and Jeha *et al*.,[14] respectively. The economic model applies a structural constraint which ensures that the per-cycle risk of death in the target population cannot be lower than that of the age- and sex-matched general population (uplifted assuming an SMR).

HRQoL is assumed to be determined by the presence or absence of disease progression and time since starting treatment. The same utility values are applied in all three treatment groups. The model includes an assumption that patients who remain alive after 5 years have a level of HRQoL which is equivalent to the EF state prior to this timepoint, regardless of the treatment received and whether they have progressed at an earlier timepoint. Utility values are adjusted for increasing age. The model also includes short-term QALY losses due to Grade 3/4 treatment-related AEs, based on AE frequency data for tisagenlecleucel, blinatumomab and FLAG-IDA reported in ELIANA,[34] von Stackelberg *et al.*[15] and Jeha *et al.,*[14] respectively. Short-term AEs are assumed to incur a disutility which is applied in the first monthly cycle of the model. Additional QALY losses are applied in the first 12 monthly cycles for those patients who undergo subsequent allo-SCT.

The model includes costs associated with: (i) pre-treatment administered prior to tisagenlecleucel infusion, including leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy (in the tisagenlecleucel group only), (ii) treatment, including procedure/drug acquisition costs, administration costs and hospitalisation costs; (iii) health state resource use; (iv) the management of AEs, including short-term events and long-term B-cell aplasia; (v) subsequent allo-SCT, and (vi) terminal care. For patients who receive the tisagenlecleucel infusion, the base case model applies NHSE CAR-T tariff costs which covers the costs of leukapheresis, CAR T-cell administration, AEs, monitoring and training costs incurred in the first 100 days following the CAR-T infusion. Treatment costs and AE costs are applied in the first model cycle. Health state costs are applied in each monthly cycle. Terminal care costs are applied as once-only costs at the point of death for patients who die within 5 years of model entry. In the company's base case analysis, health state costs and terminal care costs associated with death within 100 days post-infusion are assumed to be captured within the NHSE CAR-T tariff.

The cost-effectiveness of tisagenlecleucel versus blinatumomab and FLAG-IDA is evaluated using pairwise comparisons over an 88-year (lifetime) time horizon using monthly cycles. A full incremental analysis is not presented in the CS.[9]

5.2.3 Key assumptions employed in the company's model

The company's economic model employs the following key assumptions:

- The modelled population is 12 years of age at model entry.
- EFS and OS for tisagenlecleucel are modelled using log-logistic MCMs fitted to the observed data from ELIANA.[34]
- OS for blinatumomab and FLAG-IDA is modelled using log-normal MCMs fitted to replicated time-to-event data derived from von Stackelberg *et al*,[15] and Jeha *et al*.,[14] respectively.
- von Stackelberg *et al*,[15] and Jeha *et al*.,[14] do not report EFS data. EFS for the comparators is instead modelled by applying an HR for OS to EFS obtained from an analysis of the UK ALL study[26] to the modelled OS functions for these comparators.
- Modelled EFS and OS probabilities are structurally unrelated to the receipt of allo-SCT.
- The model includes two structural constraints: (i) the per-cycle risk of death with R/R B-cell ALL cannot be lower than that of the age- and sex-matched general population (uplifted using an SMR); (ii) the cumulative probability of EFS cannot be higher than the cumulative probability of OS at any timepoint.
- HRQoL is dependent on the presence/absence of disease progression and time since receiving treatment for R/R B-cell ALL. The model applies a higher utility value for the EF state compared with the PD state. Long-term survivors (those patients who remain alive after 5 years), are assigned the utility value for the EF state, regardless of treatment group or progression status.
- Allo-SCT is associated with a detrimental impact on HRQoL which persists for 12 months.
- AEs result in QALY losses and additional costs. The costs of short-term AEs in the tisagenlecleucel arm are assumed to be covered by NHSE CAR-T tariff.[22] Short-term AEs are assumed to be resolved by the end of the first 1-month model cycle. The model includes the costs of intravenous immunoglobulin (IVIg) replacement therapy for hypogammaglobulinaemia in tisagenlecleucel-treated patients; this is applied as a once-only cost in the first model cycle.

5.2.4 Evidence used to inform the company's model parameters

Table 30 summarises the evidence sources used to inform the model parameter values. The evidence sources and the derivation of the parameter values are described in detail in the subsequent sections.

Table 30: Summary of evidence used to inform the company's original base case model

Parameter/Group	Tisagenlecleucel group	Blinatumomab group	FLAG-IDA group
Patient characteristics	ELIANA[34]		
OS	Log-logistic MCM fitted to tisagenlecleucel group OS data from ELIANA[34] (DCO Nov 2022).	Log-normal MCM fitted to blinatumomab group OS data from von Stackelberg *et al.*[15]	Log-normal MCM model fitted to clofarabine group OS data from Jeha *et al.*[14]
EFS	Log-logistic MCM fitted to tisagenlecleucel group EFS data from ELIANA[34] (DCO Nov 2022).	Derived by applying HR from UK ALL study[26] to modelled OS function for blinatumomab.	Derived by applying HR from UK ALL study[26] to modelled OS function for FLAG-IDA.
Long-term ALL mortality risk	ONS life tables for England and Wales[72] uplifted via an SMR obtained from clinical experts.		
Subsequent allo-SCT rates	ELIANA[34] (DCO Nov 2022)	von Stackelberg *et al*.[15]	Jeha *et al*.[14]
Utility values - EF, PD and long-term survivors	Kelly *et al.*[73]		
Disutilities - short-term AEs, CRS, ICU stay and allo-SCT	Treatment-related AEs and allo-SCT disutilities from Sung *et al.*[74] CRS and non-CRS ICU stay based on assumptions. Allo-SCT disutility duration consistent with mock appraisal (Hettle *et al.*).[75]		
Utility age-adjustment	Hernández Alava *et al.*[76]		
Tisagenlecleucel decision tree probabilities	Proportions of patients who are not infused with tisagenlecleucel due to AEs, manufacturing errors or death taken from ELIANA.[34] Proportions of patients receiving pre-treatments based on ELIANA[34] and assumptions.	N/a	N/a
Pre-treatment costs	The NHSE CAR-T tariff covers the costs of leukapheresis. The costs of bridging chemotherapy and lymphodepleting chemotherapy (administration costs and hospitalisation costs) are based on NHS Reference Costs 2021/22.[77] Drug costs for bridging chemotherapy and lymphodepleting chemotherapy are taken from eMIT 2023.[78]	N/a	N/a

Parameter/Group	Tisagenlecleucel group	Blinatumomab group	FLAG-IDA group
Treatment acquisition costs	Cost of tisagenlecleucel infusion from company. Administration costs covered by NHSE CAR-T tariff.	Taken from the BNF.[79] Administration costs from NHS Reference Costs 2021/22.[77]	Costs for fludarabine and cytarabine taken from eMIT.[78] Cost of idarubicin taken from BNF.[79] Administration costs from NHS Reference Costs 2021/22.[77]
Subsequent allo-SCT costs	Stem cell harvesting costs and all procedure costs taken from NHS Reference Costs 2021/22.[77] Follow-up costs taken from UK Stem Cell Strategy Oversight Committee.[80]		
Health state costs	Resource use from ELIANA trial protocol and the NCCN. Unit costs from NHS Reference Costs 2021/22.[77]		
Short-term AEs frequencies	ELIANA[34] (DCO Nov 2022)	von Stackelberg *et al.*[15]	Jeha *et al.*[14]
Short-term AEs management costs	Covered by NHSE CAR-T tariff.[22]	NHS Reference Costs 2021/22.[77]	
CRS frequency	ELIANA[34] (DCO Nov 2022)	von Stackelberg *et al.*[15]	N/a
CRS management costs	Covered by NHS CAR-T tariff.[22]	Utilisation data (ICU days, tocilizumab doses) taken from ELIANA[34] (DCO Nov 2022). Costs of ICU stay taken from NHS Reference Costs 2021/22.[77] Tocilizumab unit cost taken from BNF.[79]	N/a
B-cell aplasia frequency	ELIANA[34] (DCO 2017)*	Kantarjian *et al*.[51]	N/a
B-cell aplasia management costs	Proportion of patients requiring IVIg based on expert opinion. Drug costs taken from BNF.[79] Administration cost taken from NHS Reference Costs 2021/22.[77] Dosing schedule based on Hettle *et al*.[75] Duration of treatment taken from ELIANA[34] (DCO Nov 2022)	N/a	N/a
Terminal care costs	NHS Reference Costs 2021/22.[77] Applied to all patients who die within first 5 years. Terminal care costs for tisagenlecleucel-treated patients who die in first 100 days assumed to be covered under the NHSE CAR-T tariff.		

FLAG-IDA - FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; OS - overall survival; EFS - event-free survival; DCO - data cut-off; HR - hazard ratio; ALL - acute lymphoblastic leukaemia; MCM - mixture-cure model; EF - event-free; PD - progressed disease; SCT - stem cell transplantation; AE - adverse event; ICU - intensive care unit; ONS - Office for National Statistics; SMR - standardised mortality ratio; CRS - cytokine release syndrome; NHSE - National Health Service England; CAR-T - chimeric antigen receptor T-cell receptor; eMIT - electronic Market Information Tool; BNF - British National Formulary; IVIg - intravenous immunoglobulin; N/a - not applicable

Note: The company's clarification response[38] (question C12) states that the proportion of patients receiving IVIg in the original model was incorrect. The company's revised model uses data from ELIANA (DCO 2022)

Patient characteristics

At model entry, patients are assumed to be 12 years of age and 43% of the population is assumed to be female, based on ELIANA.[34] Body surface area (BSA) is also based on ELIANA and is used to estimate treatment dosages for blinatumomab and FLAG-IDA. For blinatumomab, a mean BSA of 1.17m^2 was estimated based on ELIANA patients aged <18 years (age-dependent dosing) whereas for FLAG-IDA a mean BSA of 1.25m^2 was estimated based on all ELIANA patients (age-independent dosing). The EAG believes that it is counterintuitive to apply different BSA values to different comparators used in the same population; however, this does not impact on the ICERs.

Time-to-event parameters

Summary of company's parametric survival model fitting and selection process

The company fitted parametric survival models to the EFS and OS data from ELIANA[34] (DCO Nov 2022) for the tisagenlecleucel group. OS data for the comparator groups were taken from von Stackelberg *et al*.[15] for blinatumomab and Jeha *et al*.[14] for salvage chemotherapy (assuming clofarabine as a proxy for FLAG-IDA). Six standard parametric survival models were fitted to the available EFS data (including censoring for allo-SCT in ELIANA) and OS data (without censoring for allo-SCT). These included the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. These standard parametric survival models each assume a single homogenous population. The company also fitted MCMs – these models assume that the population is comprised of two discrete patient groups: (i) patients who are cured who will not die from their disease, and (ii) patients who are not cured and who have a higher risk of death due to their disease. The proportion of patients who are cured is determined by the cure fraction, which is estimated through the model-fitting procedure.

The CS[9] states that the company's model selection process included: (i) examination of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics (ii) visual inspection of the fitted survival models against the observed Kaplan-Meier survival functions and (iii) consideration of the clinical plausibility of the survival model predictions.[27]

Considerations of clinical plausibility were informed by input from three UK clinical experts who were existing or former NHS consultant haematologists, all of whom were experienced in the treatment of R/R B-cell ALL and had experience of using tisagenlecleucel. The company sent each expert a pre-read questionnaire and held subsequent discussions via a teleconference. For tisagenlecleucel, the clinical experts provided lower, upper and most likely estimates of the proportion of patients who would be expected to be event-free and alive at 1, 2, 5, 10 and 20 years as well as the proportion of patients who be expected would achieve cure. The experts were also shown the observed and predicted survival functions for ELIANA[34] and were asked to indicate which models they considered implausible and which model they preferred. For blinatumomab and FLAG-IDA, the experts were asked only to provide their expectations of the cure fraction; expectations of EFS and OS at different timepoints were not elicited from the clinical experts for these treatments.

Overall survival

OS for tisagenlecleucel-infused patients

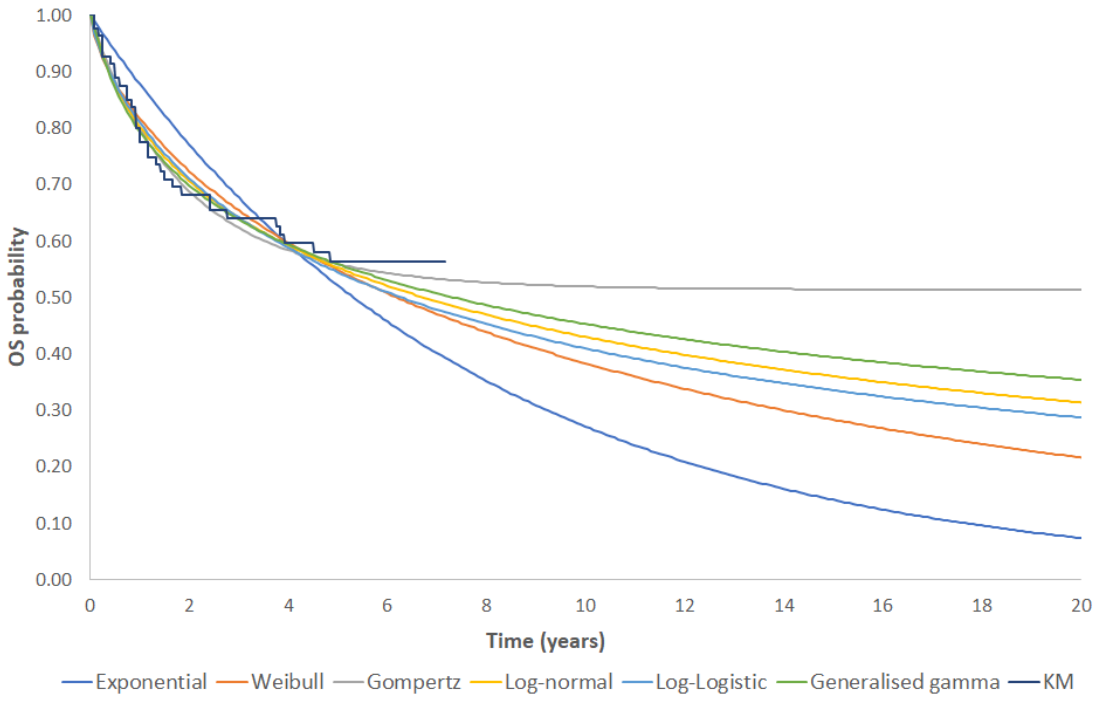
OS for patients receiving the tisagenlecleucel infusion was estimated using IPD from ELIANA[34] (DCO Nov 2022). The AIC and BIC values for the fitted survival models are shown in Table 31. Comparisons of model-predicted and observed OS for the standard parametric models and MCMs are presented in Figure 21 and Figure 22, respectively. Estimated cure fractions from the MCMs are presented in Table 32. A summary of the OS model predictions and the expectations of OS obtained from the clinical experts consulted by the company is presented in Table 33.

Table 31: AIC and BIC statistics, OS, tisagenlecleucel (ELIANA)

Distribution	Standard parametric models		Mixture-cure models	
	AIC	BIC	AIC	BIC
Exponential	366.74	369.12	**359.00**	**363.77**
Weibull	361.73	366.50	360.82	367.96
Gompertz	**358.67**	**363.44**	360.53	367.68
Log-normal	358.95	363.71	360.46	367.61
Log-logistic	360.25	365.01	360.33	367.48
Generalised gamma	360.64	367.78	362.37	371.90

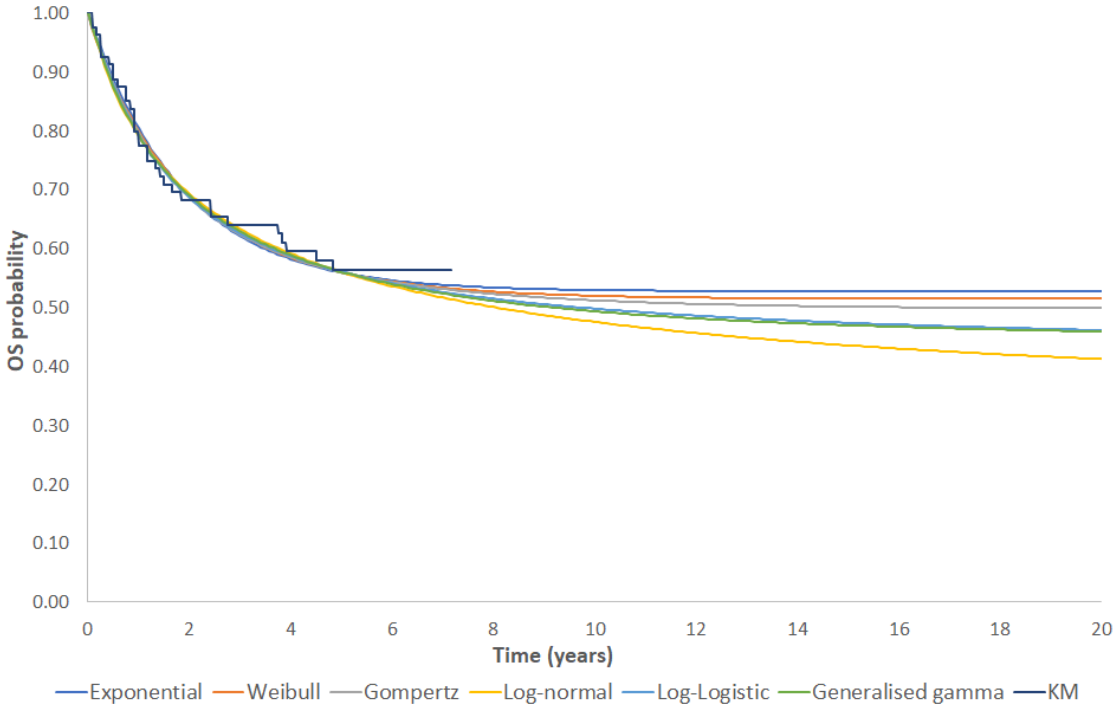
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best-fitting model highlighted in bold

Figure 21: Observed and model-predicted OS, tisagenlecleucel-infused group, standard parametric survival models (ELIANA)



Kaplan-Meier estimates provided in additional clarification response Q1. Model OS predictions generated using the company's second updated model. Survival models exclude general population mortality risks.

Figure 22: Observed and model-predicted OS, tisagenlecleucel-infused group, mixture-cure models (ELIANA)



Kaplan-Meier estimates provided in additional clarification response Q1. Model OS predictions generated using the company's second updated model. Survival models exclude general population mortality risks

Table 32: Estimated cure fractions, OS, tisagenlecleucel (ELIANA)

Distribution	Estimated cure fraction
Exponential	52.9%
Weibull	51.6%
Gompertz	41.7%
Log-normal	32.8%
Log-logistic	**42.4%**
Generalised gamma	44.4%

Table 33: Company's model predictions and clinical expert expectations, OS, tisagenlecleucel, based on ELIANA data (adapted from CS, Table 37)

Category	Model	OS probability					Cure fraction (%)
		1 year	2 years	5 years	10 years	20 years	
Kaplan-Meier estimate	-	77.4	68.1	56	-	-	-
Mean of clinicians' estimates	Lowest plausible estimate	58	48	40	30	27	25
	Most likely estimate	**76**	**68**	**54**	**47**	**42**	**40**
	Highest plausible estimate	85	75	63	57	55	56.7
Standard parametric models	Exponential	88	77	52	27	7	-
	Weibull	82	73	55	38	22	-
	Gompertz	80	69	56	52	51	
	Log-normal	80	71	56	43	32	-
	Log-logistic	81	71	55	41	29	-
	Generalised gamma	80	70	56	45	35	-
Mixture-cure models	Exponential	81	69	56	53	53	52.9
	Weibull	80	69	56	52	51	51.6
	Gompertz	80	69	56	51	50	41.7
	Log-normal	79	70	56	47	41	32.8
	Log-logistic	**79**	**69**	**56**	**50**	**46**	**42.4**
	Generalised gamma	79	69	56	49	46	44.4

The clinical experts' most likely estimate of OS and the company's selected base case parametric survival model predictions for OS are highlighted in bold
OS - overall survival

The CS[9] states that there is an apparent plateau in the OS data and that with the exception of the Gompertz model, the standard parametric survival models are unable to capture the shape of the hazard function over time. The CS states that the MCMs consistently capture this apparent plateau. Amongst the MCMs, the exponential distribution was the best-fitting model based on both the AIC and BIC. The visual fit of the models to the observed OS data from ELIANA was similar between all MCMs. The CS states that the predictions of the log-logistic and generalised gamma MCMs were most closely aligned with the clinicians' expectations of OS; the company selected the log-logistic MCM on the basis that it is more conservative than the generalised gamma MCM. The MCMs suggested a range of cure fractions – from 32.8% to 52.9%. The company's selected log-logistic MCM suggests a cure fraction of 42.4% which is in the middle of this range. The CS states that this cure fraction is well aligned to the average cure fraction estimated by the clinical experts.

The EAG notes that the log-normal MCM appears to be more closely aligned with the clinicians' expectations of survival than both the log-logistic and generalised gamma MCMs (see Table 33). This issue is discussed further in Section 5.3.

OS for blinatumomab

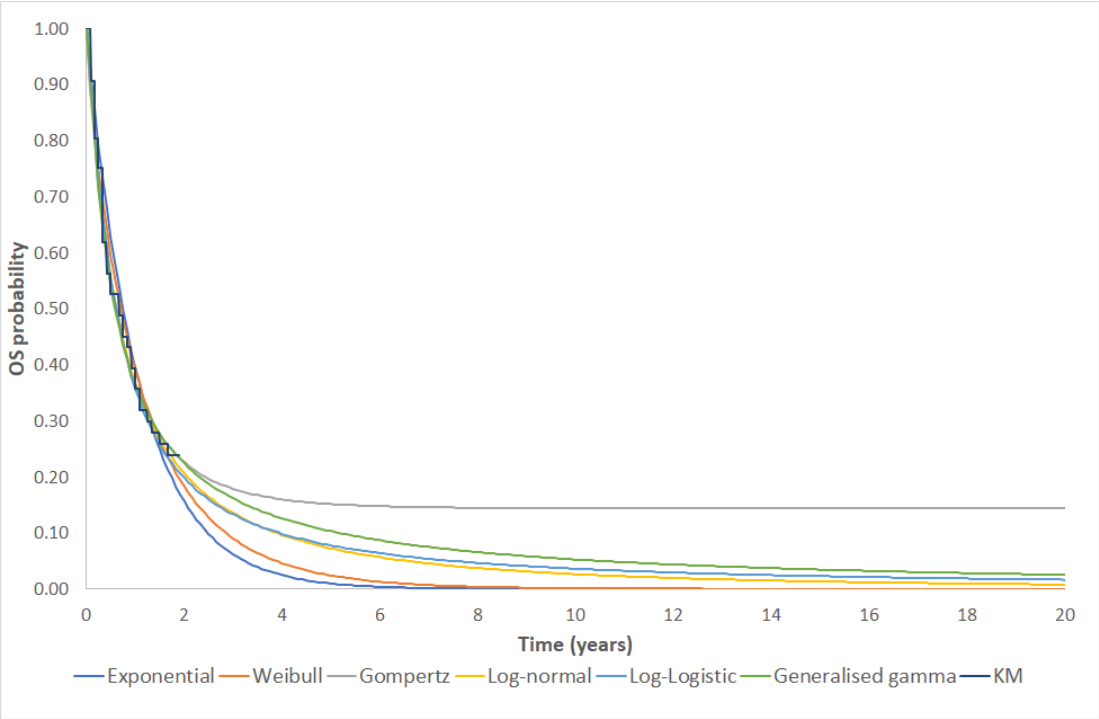
The company did not have access to the IPD from von Stackelberg *et al.*[15] Instead, the company generated pseudo-IPD for OS from this study using the algorithm reported by Guyot *et al*.[81] AIC and BIC values for the fitted models are shown in Table 34. Comparisons of model-predicted and observed OS for the standard parametric models and MCMs are presented in Figure 23 and Figure 24, respectively. Estimated cure fractions from the MCMs are presented in Table 35. The CS[9] does not report any estimates of expected OS for blinatumomab elicited from the clinical experts.

Table 34: AIC and BIC statistics, OS, blinatumomab (von Stackelberg *et al.*)

Distribution	Standard parametric models		Mixture-cure models	
	AIC	BIC	AIC	BIC
Exponential	343.79	346.04	339.62	**344.12**
Weibull	344.05	348.55	341.08	347.82
Gompertz	340.07	344.56	341.52	348.26
Log-normal	**337.83**	**342.32**	**339.19**	345.94
Log-logistic	339.31	343.81	340.23	346.98
Generalised gamma	339.12	345.87	341.12	350.11

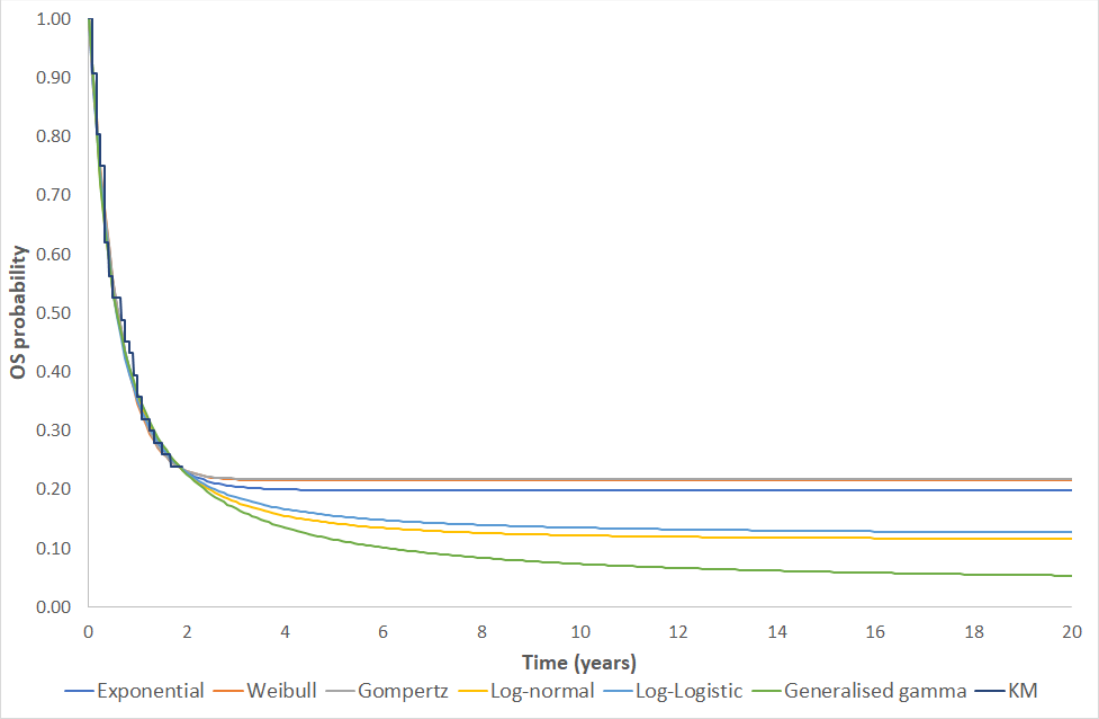
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best-fitting model highlighted in bold

Figure 23: Observed and model-predicted OS, blinatumomab group, standard parametric survival models (von Stackelberg *et al.*)



Survival models exclude general population mortality risks

Figure 24: Observed and model-predicted OS, blinatumomab group, mixture-cure models (von Stackelberg *et al.*)



Survival models exclude general population mortality risks

Table 35: Estimated cure fractions, OS, blinatumomab (von Stackelberg *et al.*)

Distribution	Estimated cure fraction
Exponential	19.8%
Weibull	21.4%
Gompertz	21.7%
Log-normal	11.4%
Log-logistic	12.1%
Generalised gamma	3.9%

The CS[9] states that amongst standard parametric survival models, the log-normal distribution was associated with the lowest AIC and BIC and that this model provides a reasonable fit to the observed data. However, the CS highlights that whilst blinatumomab alone is not considered curative, this therapy enables some patients to bridge to allo-SCT and that a proportion of transplanted patients would be expected to achieve cure. Thirty-four percent of patients in von Stackelberg *et al.*[15] received subsequent allo-SCT. Amongst the MCMs, the exponential, log-logistic and log-normal distributions had the lowest AIC and BIC values. The company selected the log-normal MCM for inclusion in the base case analysis because it had a slightly better statistical fit compared with the log-logistic MCM. The MCMs suggested cure fractions ranging from 3.9% to 21.7%. The CS states that the cure fraction estimated by the log-normal model (11.4%) was consistent with the expected proportion of patients undergoing transplant and achieving cure in the von Stackelberg *et al.* study (assuming 34.29% of patients are bridged to allo-SCT, the company received clinical advice that 40% of these would achieve cure i.e., an expected cure proportion = 13.7%).

OS for FLAG-IDA

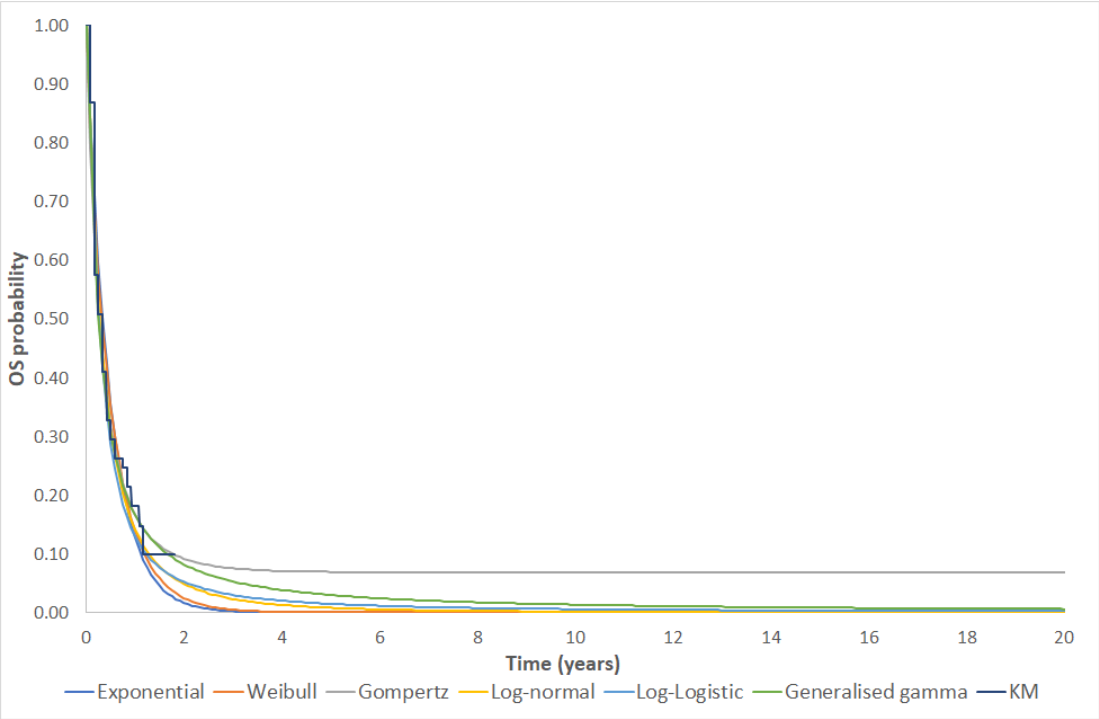
The company did not have access to IPD from Jeha *et al.*[14] As such, pseudo-IPD for OS from this study were derived using the algorithm reported by Guyot *et al.*[81] The AIC and BIC statistics for the fitted models are shown in Table 36. Comparisons of model-predicted and observed OS for the standard parametric models and MCMs are presented in Figure 25 and Figure 26, respectively. Estimated cure fractions from the MCMs are presented in Table 37.

Table 36: AIC and BIC statistics, OS, FLAG-IDA (Jeha *et al.*)

Distribution	Standard parametric models		Mixture-cure models	
	AIC	BIC	AIC	BIC
Exponential	261.42	263.53	256.68	260.90
Weibull	262.77	266.99	257.50	263.83
Gompertz	257.34	261.56	258.68	265.01
Log-normal	**252.07**	**256.29**	**251.83**	**258.16**
Log-logistic	252.87	257.09	252.69	259.02
Generalised gamma	251.93	258.26	253.59	262.03

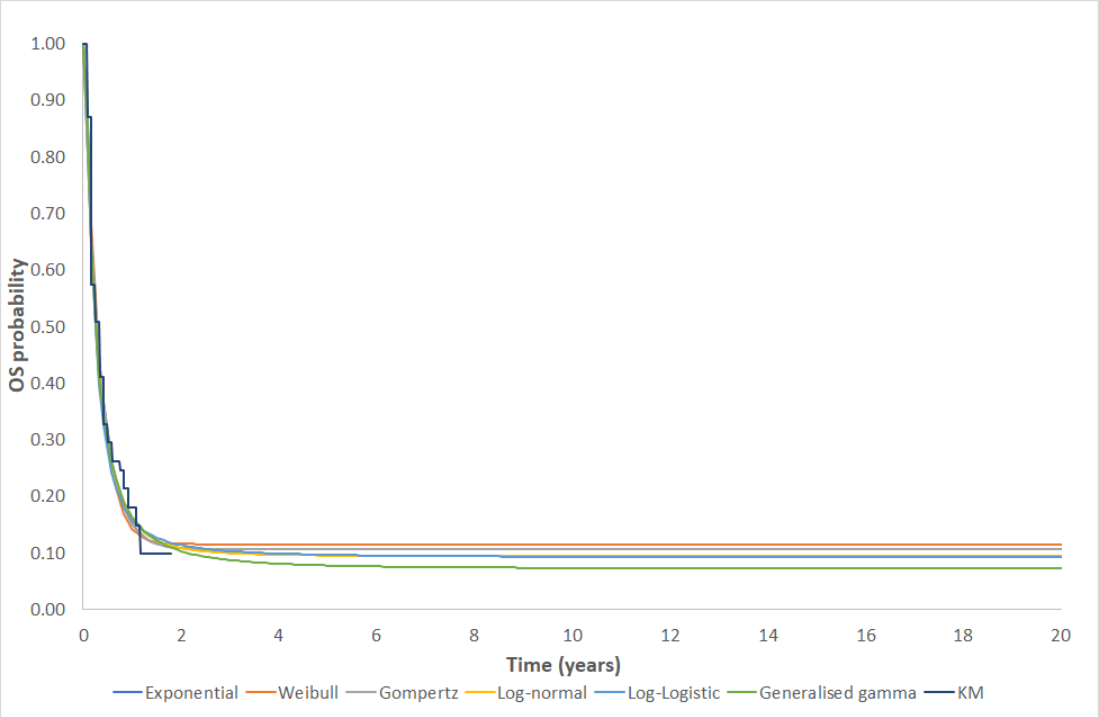
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best-fitting model highlighted in bold

Figure 25: Observed and model-predicted OS, FLAG-IDA group, standard parametric survival models (Jeha *et al.*)



Survival models exclude general population mortality risks

Figure 26: Observed and model-predicted OS, FLAG-IDA group, mixture-cure models (Jeha *et al.*)



Survival models exclude general population mortality risks

Table 37: Estimated cure fractions, OS, FLAG-IDA (Jeha *et al.*)

Distribution	Estimated cure fraction
Exponential	10.6%
Weibull	11.5%
Gompertz	10.6%
Log-normal	9.4%
Log-logistic	9.2%
Generalised gamma	7.2%

The CS[9] states that amongst the standard parametric models, the log-normal, log-logistic and generalised gamma distributions provide the best statistical fit to the observed data; however, the log-normal and log-logistic models were stated to produce an inferior fit compared with the generalised gamma distribution. As with blinatumomab, FLAG-IDA alone is not curative, but some patients may subsequently bridge to allo-SCT and a proportion of these transplanted patients would be expected to achieve cure. Amongst the MCMs, the best fitting distributions were the log-normal, log-logistic, exponential, and generalised gamma models. The MCMs suggested cure fractions ranging from 7.2% to 11.5%. The company selected the log-normal MCM for inclusion in the base case analysis because it had the best statistical fit and because the cure fraction (9.4%) was considered a conservative estimate of the expected cured population in Jeha *et al*.[14] (assuming that 14.75% of FLAG-IDA patients undergo subsequent allo-SCT and 40% of these patients achieve cure i.e., expected cured proportion = 5.9%).

Event-free survival

EFS for tisagenlecleucel-infused patients

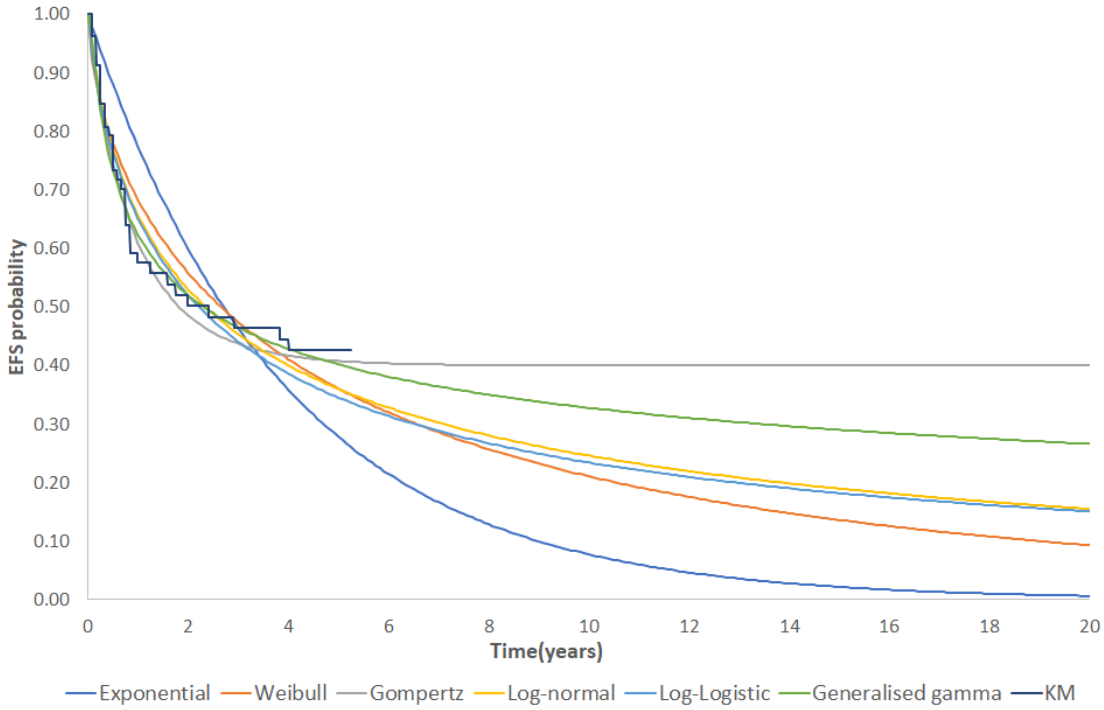
EFS for tisagenlecleucel-infused patients was estimated using IPD from ELIANA[34] (DCO Nov 2022). AIC and BIC statistics for the fitted models are summarised in Table 38. Comparisons of model-predicted and observed EFS for the standard parametric models and MCMs are presented in Figure 27 and Figure 28, respectively. Estimated cure fractions from the MCMs are presented in Table 39. A summary of model predictions and clinicians' expectations is provided in Table 40.

Table 38: AIC and BIC statistics, EFS, tisagenlecleucel (ELIANA)

Distribution	Standard parametric models		Mixture-cure models	
	AIC	BIC	AIC	BIC
Exponential	401.45	403.83	372.57	**377.34**
Weibull	386.83	391.60	374.57	381.72
Gompertz	**371.99**	**376.75**	373.71	380.85
Log-normal	377.38	382.14	371.58	378.72
Log-logistic	380.24	385.01	**371.57**	378.72
Generalised gamma	374.03	381.18	373.54	383.07

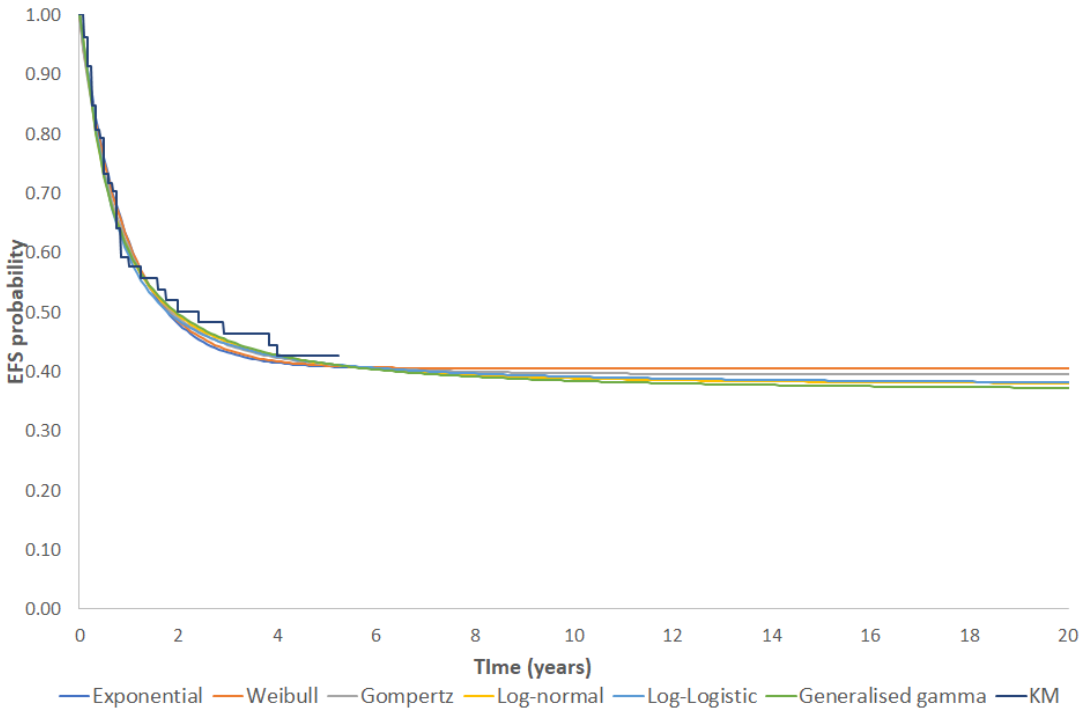
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best-fitting model highlighted in bold

Figure 27: Observed and model-predicted EFS, tisagenlecleucel group, standard parametric survival models (ELIANA)



Kaplan-Meier estimates provided in additional clarification response Q1. Model EFS predictions generated using the company's second updated model. Survival models exclude general population mortality risks

Figure 28: Observed and model-predicted EFS, tisagenlecleucel group, mixture-cure models (ELIANA)



Kaplan-Meier estimates provided in additional clarification response Q1. Model EFS predictions generated using the company's second updated model. Survival models exclude general population mortality risks

Table 39: Estimated cure fractions, EFS, tisagenlecleucel (ELIANA)

Distribution	Estimated cure fraction
Exponential	37.4%
Weibull	37.4%
Gompertz	35.0%
Log-normal	34.9%
Log-logistic	34.6%
Generalised gamma	35.6%

Table 40: Company's model predictions and clinical expert expectations, EFS, tisagenlecleucel based on ELIANA data (adapted from CS, Table 45)

Category	Model	EFS probability					Cure fraction (%)
		1 year	2 years	5 years	10 years	20 years	
Kaplan-Meier estimate	-	53.6	45.1	38	-	-	-
Mean of clinician estimates	Lowest plausible estimate	37	28	18	15	13	25
	Most likely estimate	**57**	**45**	**35**	**33**	**28**	**40**
	Highest plausible estimate	68	57	48	43	42	56.7
Standard parametric models	Exponential	76	57	25	6	0	-
	Weibull	66	53	32	18	7	-
	Gompertz	58	46	38	37	37	-
	Log-normal	63	50	32	21	12	-
	Log-logistic	63	49	31	20	12	-
	Generalised gamma	60	49	36	29	22	-
Mixture-cure models	Exponential	59	45	38	37	37	37.4
	Weibull	59	45	38	37	37	37.4
	Gompertz	58	46	38	36	36	35
	Log-normal	57	46	38	36	35	34.9
	Log-logistic	**56**	**45**	**38**	**36**	**35**	**34.6**
	Generalised gamma	57	46	38	36	35	35.6

The clinical experts' most likely estimate of EFS and the company's selected base case parametric survival model predictions for EFS are highlighted in bold
EFS - event-free survival

The CS[9] argues that there is a plateau in the EFS data from ELIANA[34] and comments that none of the standard parametric models provide a good fit to the observed data as they cannot capture the shape of hazard function over time. As such, the company fitted MCMs for EFS to align with the approach used to model OS. All of the fitted MCMs had similar AIC values, and all models except for the generalised gamma distribution had similar BIC values. All MCMs suggested similar cure fractions for EFS, ranging from 34.6% to 37.4%. The company selected the log-logistic MCM for inclusion in the base case analysis because the estimated cure fraction was considered conservative and was consistent with the clinicians' estimates (modelled cure fraction = 34.6%; clinicians' expected cure proportion = 40%).

EFS for blinatumomab and salvage chemotherapy

EFS data were not reported by von Stackelberg *et al.*[15] or Jeha *et al.*[14] As such, the company assumed that the cumulative hazard function for EFS would be proportional to the cumulative hazard function for OS. The ratio of the cumulative hazard functions between EFS and OS was modelled using data from the mitoxantrone arm of the UK ALL study (Parker *et al*.[26]). The PFS and OS Kaplan-Meier curves from this study were digitised to obtain the PFS and OS estimates at years 1, 2, 3, and 4, and the yearly estimates were logged. The company then estimated the average ratio as 0.83.

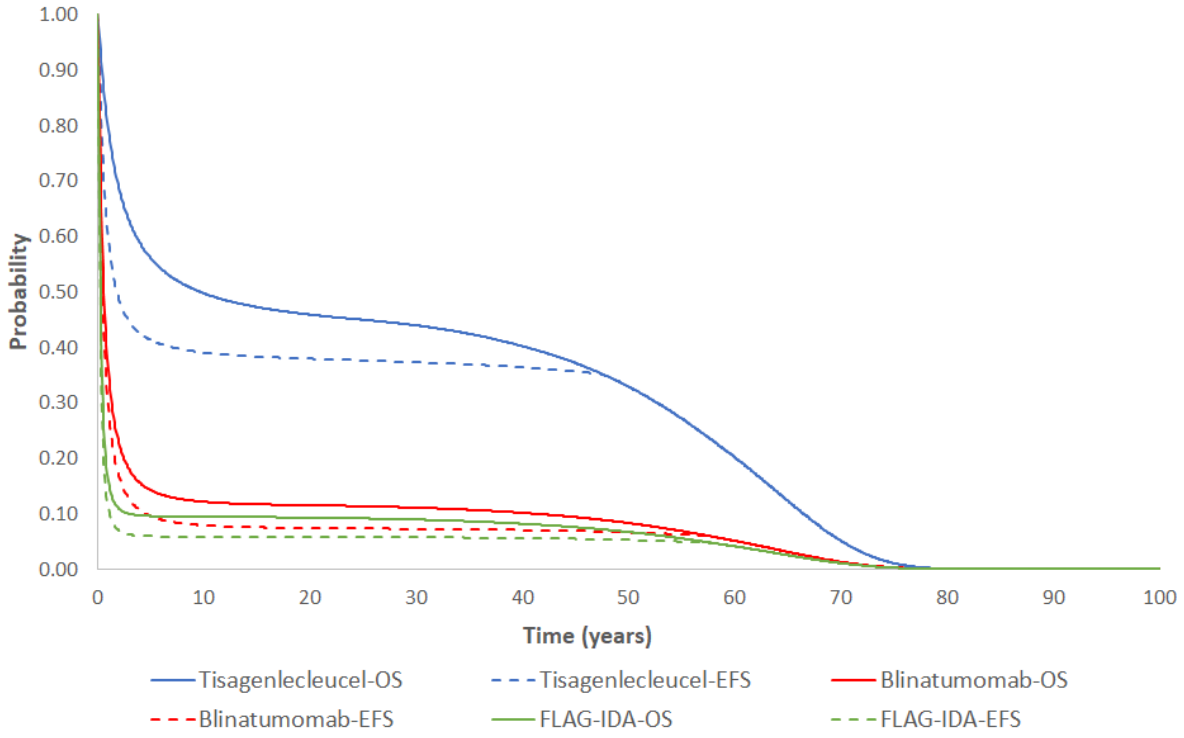
This EFS and OS relationship was assumed to continue up to five years. Subsequently, the EFS function is assumed to remain generally flat until it reaches the modelled OS function. The same ratio between EFS and OS was used for the estimation of EFS for both the blinatumomab and FLAG-IDA groups.

Summary of company's base case model predictions

Figure 29 presents a graphical summary of the overall model predictions for EFS and OS for each treatment group, based on the final model trace, including the SMR-uplifted mortality risks. The selected models are as follows:

- Tisagenlecleucel OS – log-logistic MCM
- Tisagenlecleucel EFS – log-logistic MCM
- Blinatumomab OS – log-normal MCM
- Blinatumomab EFS - log-normal MCM for blinatumomab OS + HR for OS to EFS
- FLAG-IDA OS – log-normal MCM
- FLAG-IDA EFS - log-normal MCM for FLAG-IDA OS + HR for OS to EFS.

Figure 29: Company's base case EFS and OS model predictions, all treatment groups (generated using company's model)



OS - overall survival; EFS - event-free survival; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF
Modelled functions shown in the plot reflect the final model trace including general population mortality risks uplifted using an SMR of 4.0

Health-related quality of life

ELIANA[34] included HRQoL data collection using the PedsQL and the EQ-5D. Both instruments were administered for patients aged ≥8 years old at study entry. The EQ-5D-Y was administered to children aged 8-12 years at study entry, whereas the EQ-5D-3L was administered to children aged 13 years or older at study entry. EQ-5D-3L scores were collected at baseline, Month 1 and Month 3, and then every 3 months until Month 24. ENSIGN and B2101J did not include data collection using any HRQoL instrument. Section B.3.4.1 of the CS[9] reports EQ-5D-3L estimates for patients who were event-free (EF: 30 patients; 153 assessments) and for those with progressed disease (PD: 31 patients; 50 assessments). The EF state was defined as any EQ-5D-3L on or after the treatment start date and before the date of relapse, treatment failure or death. The PD state was defined as being when patients were in an R/R state from prior treatments, or any date on or after the EFS event or before the censoring date. The EQ-5D-Y data collected in patients aged <13 years were not used. The company fitted a generalised estimating equation (GEE) model with a robust variance estimator to the available EQ-5D-3L data. The GEE model resulted in an estimated utility value for the EF state of 0.82 (standard deviation [SD]=0.22) and a utility value for the PD state of 0.66 (SD=0.36). The CS[9] states that owing to the small sample size, these data were not used in the company's base case; however, these data were included in the company's scenario analyses (see Table 49, Scenario SA4). All utility and disutility values applied in the company's base case analysis were instead drawn from the literature or assumptions.

The utility values and disutility values applied in the company's base case model are summarised in Table 41. Each source is described briefly below:

- *Health state utility values for the EF and PD health states*. The utility values for the EF and PD states were taken from a previous economic modelling study evaluating cranial radiation therapy reported by Kelly *et al*.[73] Within this study, the utility value for the EF state (utility=0.91) was derived by extracting adjusted Short Form-36 (SF-36) scores from the Swiss Childhood Cancer Survivor Study[17] and mapping them to Health Utilities Index Mark 2 (HUI-2) scores.[82] The utility value for the PD state (utility=0.75) was estimated by mapping global HRQoL scores measured using the Child Health Rating Inventory (CHRI) to the EQ-5D. Patients surviving beyond 5 years in any treatment group were assumed to have a level of HRQoL equivalent to the EF state.
- *Disutility associated with AEs of treatment*. The model applies a single disutility value of -0.42 to all Grade 3/4 AEs, regardless of their nature or site, based on a value reported in a previous modelling study reported by Sung *et al.*[74] The authors of this publication describe this value as the disutility of undergoing chemotherapy; this was estimated using a Visual Analogue Scale (VAS) which was completed by 12 physicians who care for patients undergoing bone marrow transplantation. Within the company's model, this treatment-related disutility is assumed to persist for 25.85 days, 21.00 days and 9.24 days in the tisagenlecleucel, blinatumomab and FLAG-IDA groups, respectively, based on the average duration of hospitalisation for each treatment.
- *Disutility associated with Grade 3/4 CRS.* The model assumes that patients with Grade 3/4 CRS have a utility of zero for the duration for which they are receiving treatment in ICU. The source of this assumption is not reported in the CS.[9] The model assumes a duration in ICU of 11.10 days for tisagenlecleucel and blinatumomab, respectively, based on the mean duration of ICU stays associated with CRS in ELIANA.[34]
- *Disutility associated with ICU stays (not due to CRS).* The model assumes that tisagenlecleucel-treated patients requiring ICU admission due to AEs other than CRS are associated with a utility value of zero for 1.74 days. The source of this assumption is not reported in the CS. This utility decrement is not applied in the blinatumomab or FLAG-IDA groups.
- *Disutility associated with allo-SCT.* The model applies a disutility value of -0.57 associated with allo-SCT for a period of 12 months. The EAG notes that this disutility is not linked to health state occupancy; hence, a patient who dies in the first model cycle would continue to incur the associated QALY loss until the end of the twelfth model cycle.

Health state utility values are adjusted for age using EQ-5D-3L estimates reported by Hernández Alava *et al*.[76]

Table 41: Utility and disutility values applied in the company's model

Health state/event	Mean value	Event duration (days)	Source of utility values	Measurement/ valuation method
Health state utility values				
Event-free	0.91	Mean time in EF state up to 5 years	Kelly *et al.*[73]	EF state and long-term survival states: SF-36 scores mapped to HUI-2 PD state: CHRI mapped to EQ-5D
Progressed disease	0.75	Mean time in PD state up to 5 years		
Long-term survival (applied after 5 years)	0.91	Mean time in EF or PD state after 5 years		
Disutility values				
Treatment disutility	-0.42	Tisagenlecleucel: 25.85 days Blinatumomab: 21.00 days FLAG-IDA: 9.24 days	Sung *et al.*[74]	VAS
Grade 3/4 CRS disutility	-0.91	Tisagenlecleucel: 11.10 days Blinatumomab: 11.10 days	Assumption	N/a
Other ICU stay disutility	-0.91	Tisagenlecleucel: 1.74 days	Assumption	N/a
Subsequent allo-SCT disutility	-0.57	All treatments: 365 days	Sung *et al.*[74]	VAS

EF - event-free; PD - progressed disease; CRS - cytokine release syndrome; ICU - intensive care unit; all0-SCT - allogeneic stem cell transplantation; SF-36 - Short Form 36; CHRI - Child Health Rating Inventory; HUI-2 - Health Utilities Index Mark 2; VAS - visual analogue scale; N/a - not applicable

Resource use and unit costs

The company's model includes costs associated with: (i) pre-treatment administered prior to tisagenlecleucel infusion, including leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy (in the tisagenlecleucel group only), (ii) treatment, including procedure/drug acquisition costs, administration costs and hospitalisation costs; (iii) health state resource use; (iv) the management of AEs, including short-term events and long-term B-cell aplasia; (v) subsequent allo-SCT, and (vi) terminal care. The costs applied in the company's model are summarised in Table 42; individual cost components are described in further detail below.

Table 42: Summary of main cost components in the company's base case model (cost components shaded in grey are covered by the NHSE CAR-T tariff)

Cost component	Tisagenlecleucel	Blinatumomab	FLAG-IDA
NHSE CAR-T tariff (per patient receiving infusion)	£41,101	N/a	N/a
Pre-treatment - leukapheresis	£0	N/a	N/a
Pre-treatment costs (leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy, per patient receiving the infusion*)	£10,420	N/a	N/a
Treatment costs (acquisition, administration and associated hospital stay – per patient treated)	List price £282,000 PAS price [redacted]	£89,436	£21,660
Health state costs, EF (per year)	£651 in year 1,† reducing to £27 after year 5	£263 in year 1, reducing to £27 after year 5	
Health state costs, PD (per year)	£263		
Allo-SCT (per patient transplanted)	£151,227		
Short-term AEs (per patient treated)	£0	£2,847	£1,803
IVIg treatment for B-cell aplasia (per patient treated)	£11,177‡	£0	£0
Terminal care costs (per patient dying within 5 years)	£13,198†		

FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; NHSE - National Health Service England; CAR-T - chimeric antigen receptor T-cell receptor; EF - event-free; PD - progressed disease; allo-SCT - allogeneic stem cell transplantation; AE - adverse event; PAS - Patient Access Scheme; N/a - not applicable

** Assumes 96% patients receive lymphodepleting chemotherapy*

† Excludes cost reductions applied in tisagenlecleucel group for costs covered under NHSE tariff during first 100 days post-infusion.

‡Assumes 75% of patients with hypogammaglobulinaemia require treatment with IVIg in practice. Treatment duration is assumed to be 11.4 months

Costs of pre-treatment and treatment

As described in Section 3.2, patients who receive the tisagenlecleucel infusion are assumed to undergo three pre-treatment phases: (i) leukapheresis; (ii) bridging chemotherapy and (iii) lymphodepleting therapy. The cost of leukapheresis is included in the NHSE CAR-T tariff, which is assumed to be £41,101.[22] The NHSE CAR-T tariff also covers the costs of administering the tisagenlecleucel infusion, the treatment of short-term AEs, monitoring and training for the first 100 days following the CAR-T infusion. The dosing schedule and cost breakdown for bridging chemotherapy and lymphodepleting chemotherapy prior to tisagenlecleucel, and for treatment with tisagenlecleucel and its comparators are summarised in Table 43. The base case model applies the following pre-treatment costs in the tisagenlecleucel group:

- 81.4% of patients in whom tisagenlecleucel is planned go on to receive the infusion. The model assumes that 100% of these patients receive leukapheresis, 100% receive bridging chemotherapy and 96% receive lymphodepleting chemotherapy. Only the costs of pre-treatment chemotherapy are included in the model because leukapheresis is covered by the NHSE CAR-T tariff.

- 18.6% of patients in whom tisagenlecleucel is planned do not receive the infusion, due to AEs, manufacturing error or death prior to infusion. Regardless of the reason for not receiving the infusion, the model assumes that all of these patients undergo leukapheresis and 50% of patients receive bridging chemotherapy and lymphodepleting chemotherapy. The costs of leukapheresis are included in the model for these patients.

Table 43 summarises the pre-treatments for tisagenlecleucel, together with the intervention and comparator treatments costs, including drug acquisition, administration and hospitalisation costs. Unit costs were derived from NHS Reference Costs 2021/22,[77] the Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT)[78] and the British National Formulary (BNF).[79] Dosing schedules were obtained from the SmPC for tisagenlecleucel, the ELIANA trial protocol, literature, the NHS Network Site Specific Group (NSSG) and UK clinical experts. In the company's base case model, the total cost of pre-treatment for tisagenlecleucel (excluding leukapheresis) is estimated to be £10,420 per patient receiving the infusion. The total costs of treatment are estimated to be £282,000 for the tisagenlecleucel infusion, £89,436 for blinatumomab and £21,660 for FLAG-IDA. When the PAS discount for tisagenlecleucel is included, the cost of the tisagenlecleucel infusion is [redacted]. For patients who receive the tisagenlecleucel infusion, the costs of administration are also covered by the NHSE England CAR-T tariff. In the blinatumomab group, patients are assumed to receive up to 2 cycles of blinatumomab. In the FLAG-IDA group, all patients are hospitalised following inpatient treatment with FLAG-IDA.

All pre-treatment and treatment costs are included in the base case model as once-only costs in the first model cycle. A more granular breakdown of the individual resource use estimates and costs shown in Table 43 can be found in Section B.3.5.1 of the CS.[9]

Table 43: Dosing, acquisition, administration and hospitalisation costs for pre-treatments and treatments

Drugs	Dosing schedule	Total vials/ units	Total acquisition costs	Total administration and hospitalisation costs	Source
Bridging chemotherapy					
Allopurinol	100mg/m^2 three times daily for 5 days	1	£36.50	£1,394.57	eMIT[78]
Dexamethasone	6mg/m^2 for 14 days then tapered for 7 days (assumed to receive 3mg/m^2 during tapering)	2			
Vincristine	1.5mg/m^2 IV weekly for 3 weeks	3			
Intrathecal methotrexate	12mg intrathecally on days 1 and 8	2			
Co-trimoxazole	480mg orally twice daily on 2 consecutive days each week for 3 weeks	1			
Lymphodepleting chemotherapy					
Fludarabine	30mg/m^2 IV daily for 4 doses	4	£92.37	£9,271.52	eMIT[78]
Cyclophosphamide	500mg/m^2 IV daily for 2 doses	2			
Cytarabine	500mg/m^2 IV daily for 2 days	2			
Etoposide	150 mg/m^2 IV daily for 3 days	6			
Tisagenlecleucel infusion					
Tisagenlecleucel	For patients ⩽50 kg: 0.2 to 5.0 ×10^6 CAR-positive viable T-cells per kg body weight For patients >50 kg: 0.1 to 2.5×10^8 CAR-positive viable T-cells (non-weight based)	1	£282,000	£0.00	CS[9]
Blinatumomab					
Blinatumomab for patients aged under 18 years			£71,805.20	£17,631.01	BNF[79]
Blin. cycle 1 step 1	5mcg/m^2/day on days 1-7	7			
Blin. cycle 1 step 2	15mcg/m^2/day on days 8-28	21			
Blin. cycle 2	15mcg/m^2/day on days 1-28	28			
Blinatumomab for patients aged 18 years and above					
Blin. cycle 1 step 1	9mcg/day on days 1-7	7			
Blin. cycle 1 step 2	28mcg/day on days 8-28	21			
Blin. cycle 2	28mcg/day on days 1-28	28			
Salvage chemotherapy					
Fludarabine	30mg/m^2 daily in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes (5 doses).	5	£1,413.82	£20,245.68	eMIT[78]
Cytarabine	2g/m^2 daily in 500ml sodium chloride 0.9% intravenous infusion over 4 hours (5 doses).	15			
Idarubicin	8mg/m^2 intravenous bolus daily (3 doses).	6			
G-CSF	5mcg/kg daily (12 doses).	12			

IV - intravenous; CAR - chimeric antigen receptor; G-CSF - granulocyte colony-stimulating factor; eMIT - electronic Market Information Tool; CS - company's submission; BNF - British National Formulary; blin - blinatumomab

Health state costs

The model includes health state costs which are applied during each monthly cycle. These include consultant visits, biopsies and various tests. The frequency of follow-up visits whilst patients are event-free were based on the ELIANA trial protocol[34] for the tisagenlecleucel group and the National Comprehensive Cancer Network (NCCN)[83] for the comparator groups. The follow-up schedule for patients with progressed disease was assumed to be the same for all treatment groups and was based on the follow-up schedule for patients who are event-free in year 1 in the comparator groups. Unit costs were taken from NHS Reference Costs[77] 2021/22 and the BNF.[79] These costs are assumed to be independent of treatment group; however, within the first 24 months in the base case analysis, these health state costs are applied only to patients who do not undergo subsequent allo-SCT after the initial treatment. Health state costs for patients who undergo subsequent allo-SCT are covered by the allo-SCT follow-up costs during the first 24-month period. If patients remain alive after year 5, health state costs for the EF and PD states are assumed to be the same, regardless of treatment group. Table 44 summarises the health state resource use and unit costs applied in the company's base case model.

Table 44: Summary of unit costs and follow-up schedule for health states

Cost items	Unit cost	Patients infused with tisagenlecleucel, EF - frequency				Patients receiving blinatumomab or FLAG-IDA, EF - frequency				PD - frequency
		Year 1	Year 2	Year 3-5	Year 5+	Year 1	Year 2	Year 3-5	Year 5+	All years
Consultant visit	£329.62	12	4	2	1	6	4	2	1	6
Haematology panel	£2.96	16	4	2	0	6	4	2	0	6
Coagulation panel	£2.39	3	0	0	0	0	0	0	0	0
Chemistry panel (including LFT)	£1.55	16	4	2	0	0	0	0	0	0
CSF	£380.54	1	0	0	0	1	0	0	0	1
Serum test	£2.39	5	0	0	0	0	0	0	0	0
B cell and T cell test	£2.96	8	2	2	0	0	0	0	0	0
ECG	£244.81	1	0	0	0	0	0	0	0	0
Bone marrow aspirate	£518.88	3	0	0	0	1	0	0	0	1
Bone marrow biopsy	£518.88	3	0	0	0	0	0	0	0	0
Echocardiogram	£251.86	0	0	0	0	1	0	0	0	1
LFT	£1.55	0	0	0	0	6	0	0	0	6
Total monthly cost	-	£472.58	£111.87	£56.18	£27.47	£263.00	£110.86	£55.43	£27.47	£263.00*

EF - event-free; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; PD - progressed disease; LFT - liver function test; CSF - cerebrospinal fluid; ECG - electrocardiogram
** Health state costs for tisagenlecleucel-treated patients in PD in year 1 are £191 to account for follow-up costs already covered under the NHSE CAR-T tariff*

AE management costs

The company's model includes costs related to the management of AEs based on event frequencies derived from ELIANA[34] for the tisagenlecleucel group, von Stackelberg *et al.*[15] for the blinatumomab group and Jeha *et al.*[14] for the FLAG-IDA group. The unit costs of managing AEs were derived from NHS Reference Costs 2021/22.[77] A summary of the AE frequencies and unit costs applied in the model is provided in Table 45. The model considers short-term and long-term AEs separately when calculating costs. In the base case model, the costs of short-term AEs (including CRS) in the tisagenlecleucel group are already covered under the NHSE CAR-T tariff.[22]

Table 45: Summary of AE frequencies and management costs

AEs	Frequency			Unit cost
	Tisagenlecleucel	Blinatumomab	FLAG-IDA	
Short-term AEs				
Acute kidney injury	10.13%	0.00%	0.00%	£1,673.83
Alanine aminotransferase increased	8.86%	0.00%	15.71%	£409.24
Anaemia	11.39%	0.00%	35.71%	£368.84
Anorexia	0.00%	19.67%	0.00%	£625.37
Aspartate aminotransferase increased	13.92%	0.00%	11.43%	£409.24
Bacteraemia	2.53%	13.11%	0.00%	£456.64
Blood bilirubin increased	11.39%	0.00%	0.00%	£732.39
Cytokine-release syndrome	48.10%	0.00%	5.71%	£35,142.62†
Decreased appetite	15.19%	0.00%	0.00%	£625.37
Dermatitis	0.00%	11.48%	0.00%	£607.16
Diarrhoea	2.53%	13.11%	0.00%	£643.90
Encephalopathy	5.06%	0.00%	0.00%	£513.09
Epistaxis	1.27%	13.11%	0.00%	£2,937.95
Febrile neutropenia	34.18%	49.18%	17.14%	£529.09
Hallucination	0.00%	13.11%	0.00%	£282.85
Hepatomegaly	1.27%	11.48%	0.00%	£388.08
Hyperglycaemia	6.33%	0.00%	0.00%	£390.03
Hypertension	6.33%	9.84%	5.71%	£390.85
Hypocalcaemia	6.33%	0.00%	0.00%	£384.92
Hypogammaglobulinemia	7.59%	0.00%	0.00%	£384.92
Hypokalaemia	13.92%	0.00%	17.14%	£384.92
Hypophosphatemia	11.39%	0.00%	0.00%	£384.92
Hypotension	20.25%	18.03%	0.00%	£390.85
Hypoxia	20.25%	0.00%	0.00%	£575.45
Infection	49.37%	9.84%	0.00%	£770.54
Leukopenia	2.53%	0.00%	10.00%	£384.82
Lymphocyte count decreased	18.99%	0.00%	0.00%	£384.82
Nausea	2.53%	16.39%	0.00%	£650.11
Neutropenia	11.39%	14.75%	17.14%	£384.82
Neutrophil count decreased	26.58%	0.00%	12.86%	£384.82
Petechiae	0.00%	11.48%	0.00%	£446.28
Platelet count decreased	18.99%	0.00%	14.29%	£381.27
Pleural effusion	3.80%	9.84%	0.00%	£599.27
Pneumonia	5.06%	9.84%	0.00%	£634.36

Pulmonary oedema	8.86%	0.00%	0.00%	£599.27
Pyrexia	13.92%	14.75%	14.29%	£622.53
Respiratory distress	1.27%	11.48%	0.00%	£575.45
Sepsis	3.80%	13.11%	0.00%	£456.64
Thrombocytopenia	11.39%	0.00%	21.43%	£381.27
White blood cell count decreased	21.52%	0.00%	10.00%	£384.82
Long-term AEs				
B-cell aplasia (hypogammaglobulinaemia)	73.33%	0.00%	0.00%	£20,322*

AE - adverse event; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF
** Cost of treating one patient with IVIg for a duration of 11.4 months. The latest version of the company's revised model applies this cost to 75% of 40.5% of patients experiencing hypogammaglobulinaemia*
†Assumes treatment with tocilizumab plus a paediatric ICU admission for a duration of 11.1 days
For tisagenlecleucel, the values were based on grade 3 to 4 AEs, regardless of study drug relationship, occurring any time post tisagenlecleucel infusion in > 5% of patients.
For blinatumomab, the values were based on AEs of worst grade ≥3 regardless of relationship to treatment that occurred in ≥5% of patients (who received the recommended dose of 5/15 µg/m^2/day in phase I or II) during the treatment period and until 30 days after the last treatment or before allogeneic hematopoietic stem-cell transplantation or start of chemotherapy.
For FLAG-IDA, the values were based on grade ≥3 AEs, regardless of causality that occurred in ≥10% of patients in all cycles.

Hypogammaglobulinaemia resulting from B-cell aplasia is considered as a long-term AE for patients who receive the tisagenlecleucel infusion. The cost of treating hypogammaglobulinaemia is included as a single lump sum cost in the first model cycle. The company's original model assumed that 73.33% of patients infused with tisagenlecleucel experience B-cell aplasia, based on ELIANA (Nov 2022 data cut-off). The CS states that an estimated 75% of patients with hypogammaglobulinemia will receive IVIg in NHS practice. Therefore, 55% of patients treated with tisagenlecleucel were assumed to incur the costs of IVIg. The median IVIg treatment duration was based on the median time to B-cell recovery in ELIANA (DCO 2017). The IVIg dosing schedule was derived from a NICE mock appraisal by Hettle *et al*.,[75] unit costs were taken from the BNF[79] and the administration cost was taken from NHS Reference Costs 2021/22[77] (see Table 46). The company's clarification response (question C12) highlights that the original model was subject to an error as it included all patients receiving IVIg (73.3%), rather than the proportion of patients with hypogammaglobulinaemia (40.5%); the company's revised model includes a lower expected cost of IVIg of £6,173 per patient receiving tisagenlecleucel.

Table 46: Cost assumptions for hypogammaglobulinaemia

	Dosing	**Pack size**	**Price per vial**	**No. vials/ infusion**	**No. infusions/ cycle**	**Monthly drug cost**	**Monthly admin cost**	**Treatment duration (months)**
IVIg package 1	500mg/ kg per month	10,000mg	£700.00	2	1	£1,575.00	£207.59	11.40
IVIg package 2		2,500mg	£175.00	1				
Total IVIg cost per patient experiencing hypogammaglobulinemia								£20,322
Expected cost of IVIg for hypogammaglobulinemia per patient receiving the infusion (original model)								£11,177
Expected cost of IVIg for hypogammaglobulinemia per patient receiving the infusion (latest revised model)								£6,173

IVIg - intravenous immunoglobulin

Subsequent allo-SCT costs

The assumed costs of subsequent SCT are shown in Table 47. These costs are applied only to the proportion of patients who receive allo-SCT after their initial treatment: 22.78% for the tisagenlecleucel group; 34.29% for the blinatumomab group, and 14.75% for the FLAG-IDA group. Follow-up costs for allo-SCT are assumed to continue for 24 months, and during that period it is assumed that the health state follow-up costs for patients in the EF and PD states are already included in the allo-SCT follow-up costs.

Table 47: Cost breakdown of subsequent allo-SCT

Description	Cost	Source
Stem cell harvesting cost	£5,441.44	NHS Reference Costs 2021/22[77]
Allo-SCT procedure	£102,040.46	NHS Reference Costs 2021/22[77]
Allo-SCT follow-up costs (up to 6 months)	£28,390 £25,551 (weighted cost for 90% alive)	UK Stem Cell Strategy Oversight Committee.[80] Costs are from 2012/13 cost year and are weighted by the proportion of people alive at each time point. Total costs are inflated to current prices.
Allo-SCT follow-up costs (6 to 12 months)	£19,502 £9,361 (weighted cost for 48% alive)	
Allo-SCT follow-up costs (12 to 24 months)	£14,073 £4,363 (weighted cost for 31% alive)	
Total allo-SCT follow-up costs in 2021/22 cost year	£43,745.53	
Total cost per patient undergoing allo-SCT	**£151,227.43**	-

allo-SCT – allogeneic stem cell transplantation

Terminal care costs

The company's model applies terminal care costs only for patients who die within 5 years of model entry. These are applied as a once-only cost of £13,198 which was estimated based on the weighted mean of non-elective long stay paediatric ALL episodes with a length of stay 1 day or more from NHS Reference Costs 2021/22.[77] Within the tisagenlecleucel group, terminal care costs for patients who die during the first 100 days after receiving the infusion are assumed to be covered by NHSE CAR-T tariff.

5.2.5 Model evaluation methods

The CS[9] presents cost-effectiveness results for tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). Results are presented at the list price and the PAS price, each including or excluding a severity modifier of 1.7.

The CS[9] presents the results of deterministic sensitivity analyses (DSAs) in graphical form using tornado plots. The CS also presents the results of 15 probabilistic scenario analyses which explore alternative values for: discount rates; subsequent allo-SCT rates; utility and disutility values, the duration of ICU days for CRS; the SMR; cost items included in the NHSE CAR-T tariff; costs of IVIg treatment costs in the blinatumomab group; and the proportion of IVIg treatment recipients in the tisagenlecleucel group. These scenario analyses also include the use of some alternative parametric survival distributions for EFS and OS.

5.2.6 *Company's original model results*

This section presents the results of the company's base case analysis and sensitivity analyses generated using the original submitted model. All results presented in this section exclude the severity modifier and reflect discount rates for health outcomes and costs of 3.5%, unless otherwise stated. All results include the PAS discount for tisagenlecleucel.

Company's central estimates of cost-effectiveness

The company's base case results are presented in Table 48. Compared with blinatumomab, the probabilistic version of the model suggests that tisagenlecleucel is expected to generate an additional [redacted] QALYs at an incremental cost of [redacted] per patient; the corresponding ICER is expected to be £20,410 per QALY gained. Compared with FLAG-IDA, the probabilistic version of the model suggests that tisagenlecleucel is expected to generate an additional [redacted] QALYs at an incremental cost of [redacted] per patient; the corresponding ICER is expected to be £30,031 per QALY gained. The ICERs generated using the deterministic model are similar, although the EAG notes that there is a noticeable difference between the incremental QALYs generated using the probabilistic and deterministic versions of the model; these apparent discrepancies appear to be driven by uncertainty around the modelled cure fractions for blinatumomab and FLAG-IDA, and by all of the MCM parameters for tisagenlecleucel.

The EAG notes that all results presented in the CS[9] are pairwise in nature. If the company had undertaken fully incremental analyses, blinatumomab would have been ruled out of the analysis due to extended dominance by tisagenlecleucel and FLAG-IDA.

Table 48: Company's original base case model results, pairwise comparisons of tisagenlecleucel versus blinatumomab and FLAG-IDA, includes tisagenlecleucel PAS, excludes QALY weighting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER	DM
Probabilistic model†								
Tisagenlecleucel	23.89	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	8.50	3.93	£157,381	15.40	[redacted]	[redacted]	**£20,410**	1.7
FLAG-IDA	5.98	2.64	£59,992	17.91	[redacted]	[redacted]	**£30,031**	1.7
Deterministic model								
Tisagenlecleucel	22.98	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	7.33	3.06	£158,289	15.65	[redacted]	[redacted]	**£19,218**	1.7
FLAG-IDA	5.55	2.22	£59,980	17.43	[redacted]	[redacted]	**£30,778**	1.7

** Undiscounted*
† Results generated by the EAG r-running the PSA sub-routine
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF

Company's PSA results

CEACs for tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA are presented in Figure 30 and Figure 31, respectively. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the company's model suggests that the probability that tisagenlecleucel generates more net benefit than blinatumomab is approximately 0.50 and 0.84, respectively. At these same WTP thresholds, the company's model suggests that the probability that tisagenlecleucel generates more net benefit than FLAG-IDA is approximately 0.03 and 0.48, respectively.

Figure 30: CEACs, tisagenlecleucel versus blinatumomab, pairwise comparison, includes tisagenlecleucel PAS, excludes QALY weighting

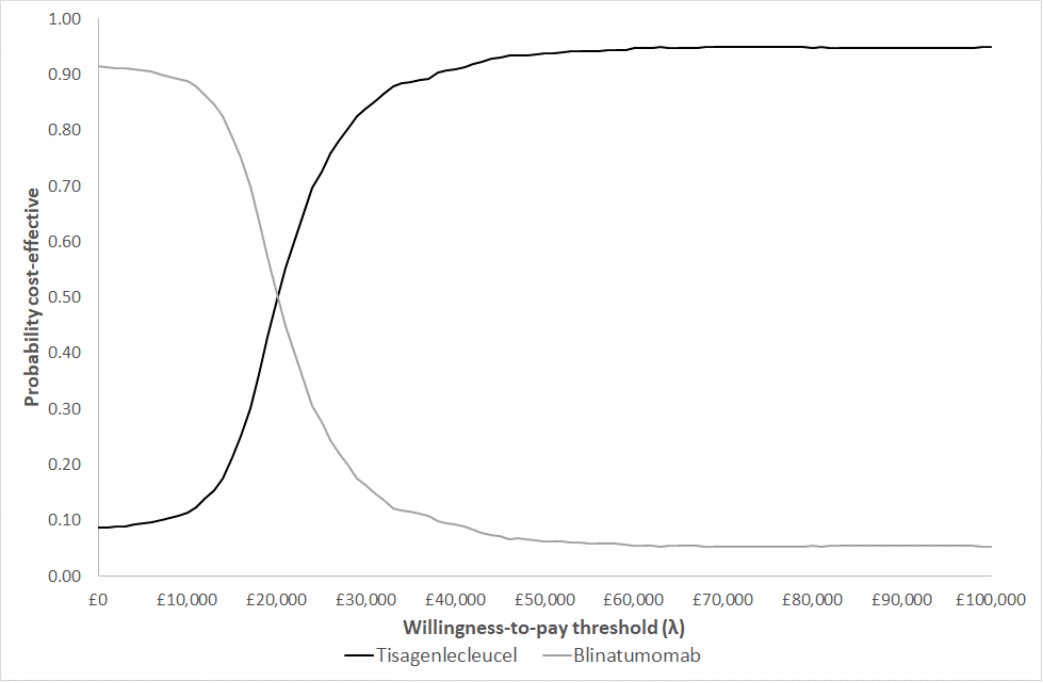
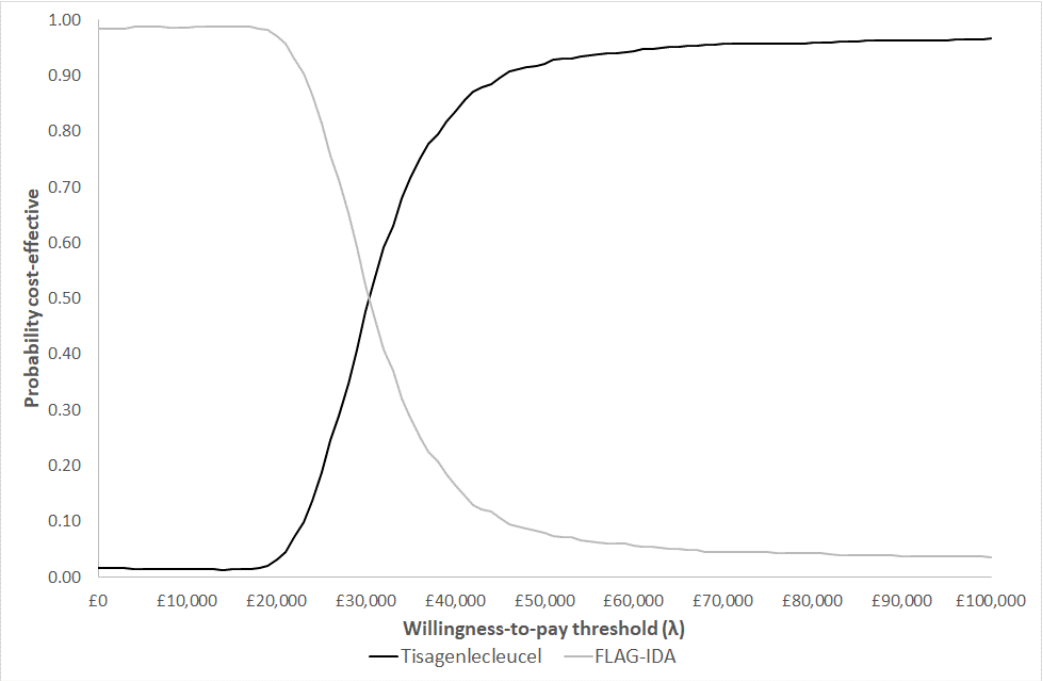


Figure 31: CEACs, tisagenlecleucel versus FLAG-IDA, pairwise comparison, includes tisagenlecleucel PAS, excluding QALY weighting



Company's DSA results

The results of the company's DSAs for tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA are presented in Figure 32 and Figure 33, respectively. For the comparison against blinatumomab, the DSAs indicate that the ICER is influenced most by the costs of the comparator and by the subsequent allo-SCT rate in both treatment groups; however, the ICER remains lower than £22,000 per QALY gained across all analyses. For the comparison against FLAG-IDA, the DSAs indicate that the ICER is somewhat sensitive to the utility value for the EF state, the subsequent allo-SCT rate in both treatment groups and the administration/hospitalisation cost for tisagenlecleucel; the highest ICER generated from the DSAs is estimated to be £32,615 per QALY gained.

Figure 32: Company's DSA results, tisagenlecleucel versus blinatumomab, includes tisagenlecleucel PAS, excludes QALY weighting

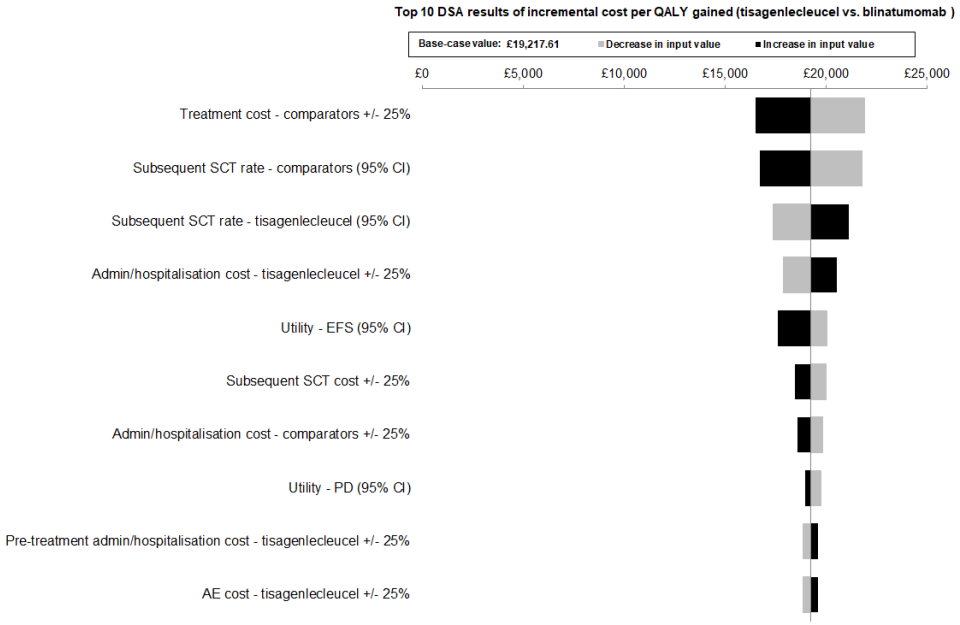
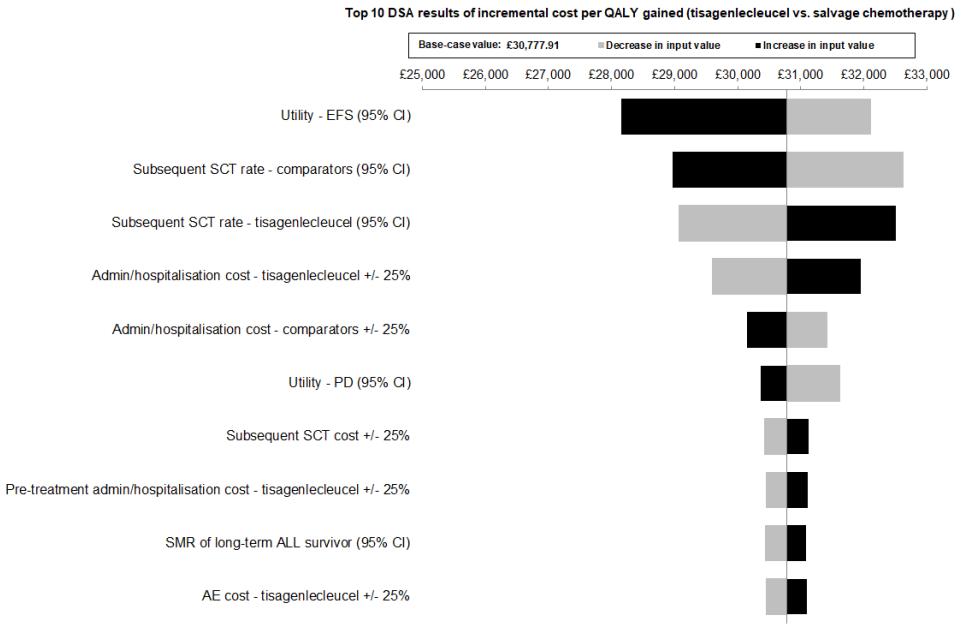


Figure 33: Company's DSA results, tisagenlecleucel versus FLAG-IDA, includes tisagenlecleucel PAS, excludes QALY weighting



Company's scenario analyses

The results of the company's probabilistic scenario analyses are presented in Table 49. For the comparison against blinatumomab, the ICERs are in the range £13,365 to £26,227 per QALY gained. For the comparison against FLAG-IDA, the ICERs are in the range £20,444 to £33,448 per QALY gained.

Table 49: Company's probabilistic scenario analyses, pairwise comparisons, includes tisagenlecleucel PAS, excludes QALY weighting

Scenario no.	Scenario description	Tisagenlecleucel versus blinatumomab			Tisagenlecleucel versus FLAG-IDA		
		Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER
-	Base case	[redacted]	[redacted]	**£19,449**	[redacted]	[redacted]	**£29,759**
SA1	Tisagenlecleucel OS: Log-normal	[redacted]	[redacted]	**£19,476**	[redacted]	[redacted]	**£29,104**
SA2	Tisagenlecleucel OS: Gompertz	[redacted]	[redacted]	**£13,694**	[redacted]	[redacted]	**£21,641**
SA3	Blinatumomab OS: Log-logistic	[redacted]	[redacted]	**£20,324**	[redacted]	[redacted]	**£30,032**
SA4	Utility values from ELIANA	[redacted]	[redacted]	**£22,247**	[redacted]	[redacted]	**£33,448**
SA5	ELIANA utility for first 2 years (no treatment or AE disutilities applied)	[redacted]	[redacted]	**£21,943**	[redacted]	[redacted]	**£33,153**
SA6	Allo-SCT disutility from Sung *et al.* (-0.57) for three months followed by Felder-Puig *et al.* (-0.13) for 9 months	[redacted]	[redacted]	**£19,757**	[redacted]	[redacted]	**£29,877**
SA7	All patients experiencing hypogammaglobulinaemia receive IVIg	[redacted]	[redacted]	**£20,503**	[redacted]	[redacted]	**£30,382**
SA8	Patients receiving blinatumomab assumed to receive IVIg	[redacted]	[redacted]	**£19,659**	[redacted]	[redacted]	**£30,152**
SA9	Duration of CRS-related ICU admission based on clinician estimates	[redacted]	[redacted]	**£19,981**	[redacted]	[redacted]	**£29,673**
SA10	Vial sharing assumed	[redacted]	[redacted]	**£26,227**	[redacted]	[redacted]	**£29,786**
SA11	Resource use source: NHS reference costs	[redacted]	[redacted]	**£21,564**	[redacted]	[redacted]	**£31,606**
SA12	Tocilizumab discount assumed to be 20%	[redacted]	[redacted]	**£19,689**	[redacted]	[redacted]	**£29,669**
SA13	SMR adjustment = 9.05	[redacted]	[redacted]	**£20,933**	[redacted]	[redacted]	**£30,581**
SA14	Discount rate = 1.5% applied	[redacted]	[redacted]	**£13,365**	[redacted]	[redacted]	**£20,444**
SA15	Tisagenlecleucel subsequent allo-SCT rate from NDRS report	[redacted]	[redacted]	**£18,191**	[redacted]	[redacted]	**£28,645**

PAS - Patient Access Scheme; inc. - incremental; QALYs - quality-adjusted life year; OS - overall survival; allo-SCT - allogeneic stem cell transplantation; CRS - cytokine release syndrome; IVIg - intravenous immunoglobulin; NHS - National Health Service; NDRS - National Disease Registration Service

5.3 Critical appraisal

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.[9] As part of their response to clarification questions from the EAG,[38] the company submitted two revised versions of the model which include the correction of minor errors and additional functionality to undertake additional analyses requested by the EAG. The second revised model and its results are summarised separately in Section 5.4.

5.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[62, 84]
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[9] and the company's executable model.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 Model verification by the EAG

The EAG rebuilt the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 50, the results obtained from the EAG's double-programmed model are very similar to those generated using the company's model. During the process of rebuilding the model, the EAG identified several minor programming errors: these are described further in Section 5.3.5. The correction of these errors forms part of the EAG's exploratory analysis (see Section 5.6).

Table 50: Comparison of results generated using the company's original model and the EAG's double-programmed model (excludes the correction of errors identified by the EAG)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's deterministic model							
Tisagenlecleucel	22.98	[redacted]	[redacted]	-	-	-	-
Blinatumomab	7.33	3.06	£158,289	15.65	[redacted]	[redacted]	**£19,218**
FLAG-IDA	5.55	2.22	£59,980	17.43	[redacted]	[redacted]	**£30,778**
EAG's double-programmed model							
Tisagenlecleucel	22.98	[redacted]	[redacted]	-	-	-	-
Blinatumomab	7.33	3.06	[redacted]	15.65	[redacted]	[redacted]	**£19,099**
FLAG-IDA	5.55	2.22	[redacted]	17.43	[redacted]	[redacted]	**£30,777**

** Undiscounted*
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EAG - External Assessment Group

5.3.3 Correspondence of the model inputs and the original sources of parameter values

Where possible, the EAG checked the company's model input values against their original sources. The parameters of the survival models were generated from analyses of IPD or pseudo-IPD from the ELIANA trial,[34] von Stackelberg *et al.*,[15] and Jeha *et al.*,[14] which were not made available to the EAG; as such, the EAG cannot verify that these analyses have been undertaken appropriately. The EAG was able to identify most of the other model parameter values including the utility and disutility values, decision tree probabilities, AE rates and most of the unit costs. However, the EAG was unable to identify the proportion of patients requiring hospitalisation for lymphodepleting chemotherapy, BSA estimates, outpatient and ICU days to administer tisagenlecleucel, and the cost of idarubicin reported in the CS.

During the factual accuracy check stage of the appraisal, the company clarified that the cost of idarubicin used in the model could not be identified by the EAG because this unit cost was updated in the BNF after the CS was submitted to NICE.

5.3.4 Adherence to NICE Reference Case

Table 51 summarises the extent to which the company's economic model adheres to the NICE Reference Case.[33] Overall, the EAG believes that the company's model is partly in line with the Reference Case. The most pertinent deviations relate to: (i) the exclusion of comparators listed in the final NICE scope;[29] (ii) the use of naïve ITCs; (iii) the use of pairwise rather than fully incremental cost-utility analyses, and (iv) the inclusion of utility values which have not been derived using the EQ-5D-3L. The EAG notes that all of these issues were also present in TA554.[19]

Table 51: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The company's analysis is partly in line with the final NICE scope.[29] The model compares tisagenlecleucel versus blinatumomab and FLAG-IDA. No comparison is made against inotuzumab ozogamicin, TKIs, allo-SCT or BSC.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health outcomes accrued by patients. Health impacts on caregivers are not included.
Perspective on costs	NHS and PSS	Costs reflect those borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach. A fully incremental analysis is not presented in the CS.[9]
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model includes an 88-year (lifetime) horizon. At the end of the time horizon, virtually all (>99.99%) patients in all treatment groups have died.
Synthesis of evidence on health effects	Based on systematic review	The company undertook an SLR to identify evidence on the clinical effectiveness of treatments within the target population (CS, Appendix D[39]). The EAG notes three key issues: (1) Whilst there are three tisagenlecleucel studies within this population, outcomes for the tisagenlecleucel group of the model are informed only by ELIANA.[34] (2) The company's SLR identified several studies reporting outcomes for comparator therapies. The company's model uses von Stackelberg *et al.*[15] for blinatumomab and Jeha *et al.*[14] for FLAG-IDA. Other studies may be more relevant. (3) Relative treatment effects are informed by naïve ITCs.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	The company's model uses utility values derived from published literature[73, 74] and additional assumptions. The utility value for the EF state is based on the HUI-2 rather than the EQ-5D-3L. The disutility values for allo-SCT and treatment-related AEs are based on VAS estimates rather than the EQ-5D-3L. The impact of time spent in ICU is based on assumptions.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	The company's model suggests estimates of QALY shortfall which lead to a decision modifier of 1.7 for both pairwise comparisons.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The model includes costs which are relevant to the NHS and PSS. Unit costs are taken from the literature, routine costing sources and the NHSE CAR-T tariff.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5%. Results are also presented using non-reference case discount rates of 1.5%.

HTA - health technology assessment; NICE - National Institute for Health and Care Excellence; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; allo-SCT - allogeneic stem cell transplantation; BSC - best supportive care; PSS - Personal Social Services; CS - company's submission; EQ-5D - Euroqol 5-Dimensions; HRQoL - health-related quality of life; EF - event-free; VAS - visual analogue scale; AE - adverse event; CRS - cytokine release syndrome; QALY - quality-adjusted life year; NHSE - National Health Service England; CAR-T - chimeric antigen receptor T-cell receptor

5.3.5 Main issues identified from the EAG's critical appraisal

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's original economic analysis for this appraisal. These issues are discussed in further detail in the subsequent sections. Where relevant, the EAG draws reference to key issues raised by the ERG in TA554, as well as the Appraisal Committee's conclusions as described in the final guidance document for this previous appraisal.[19] Some, but not all, of these issues are addressed in the company's revised model (see Section 5.4).

Box 1: Main issues identified from the critical appraisal

(1)	Model errors
(2)	Use of ELIANA data in preference to the pooled tisagenlecleucel dataset
(3)	EFS definition in the tisagenlecleucel studies may exaggerate benefits
(4)	Uncertainty relating to costs and outcomes for patients who do not receive the tisagenlecleucel infusion
(5)	Uncertainty around relative effectiveness of tisagenlecleucel versus comparators
(6)	Issues relating to the company's survival analysis
(7)	Uncertainty around excess mortality risks in cured patients
(8)	Issues relating to the utility and disutility values applied in the company's model
(9)	Issues relating to resource use and costs applied in the company's model

(1) Model errors

The EAG's double-programming exercise and additional cell-checking revealed seven errors in the company's original executable model. These are described briefly below.

(a) General population mortality risks

The company's model uses general population life tables in two ways: (a) to determine per-cycle mortality risks in patients who are cured and (b) to constrain the overall per-cycle mortality risk both for patients who are cured and for those who die as a consequence of their ALL. Within the calculations used to derive these general population mortality constraints, the model assumes that the proportionate split of men and women remains constant at every age; however, the general population life tables indicate that men and women have different age-specific risks of death. Both of these cannot simultaneously be true. The EAG believes that it would be more appropriate to estimate general population mortality risks using a weighted survival model, based on separate survival models for men and women, with the weighting applied at baseline.

(b) Minor error in the lookup function applied to SMR-uplifted life tables

Patients enter the model aged 12 years. During each model cycle, the per-cycle risk of death for the mix of surviving cured and uncured patients with R/R B-cell ALL is constrained by the mortality risk for the age- and sex-matched general population, uplifted by an SMR of 4.0 (as described in point (a) above). The mortality risk for 12-year-olds is applied for 11 monthly cycles rather than 12 monthly cycles (i.e., all SMR-uplifted life table risks are erroneously offset by one month).

(c) Lack of general population mortality constraint on the per-cycle risk of EFS

EFS is a composite endpoint which includes both relapse/progression and death due to any cause. The company's model constrains the cumulative probability of EFS by the cumulative probability of OS using an =MIN() function; this ensures that the cumulative EFS function cannot exceed the cumulative OS function at any timepoint. However, the company's model does not constrain the per-cycle risk of EFS events by the general population mortality risk – this implies that at some timepoints, the joint risk of relapse or death for people with non-relapsed ALL is lower than the risk of death in the SMR-uplifted general population. The EAG believes that it would be more appropriate to constrain the per-cycle EFS risks by the SMR-uplifted general population mortality risk.

(d) Inconsistent application of SMR to the life tables

The company's model trace calculations apply general population mortality risks from life tables in two ways: (i) the life table risks (excluding an SMR) are applied to the cured group in the survivor function for the MCM, and (ii) SMR-uplifted life table mortality risks are applied as a constraint to the overall MCM in the model trace (which affects all surviving cured and non-cured patients). The EAG considers it to be more consistent to apply the same SMR-uplifted mortality risks as a constraint for survival in the non-cured group and to characterise the risk of death in the cured group of the MCM.

(e) Use of inappropriate life tables

As noted in Table 30, the company's model uses life tables for England and Wales from the Office for National Statistics (ONS). The model should use life tables for England only.

(f) The disutility associated with allo-SCT is not linked to the model trace

The company's model assumes that allo-SCT is associated with a constant QALY loss in each of the first 12 monthly cycles. However, the disutility value associated with allo-SCT is not linked to the probability of a patient being in the alive health states. This means that patients who undergo allo-SCT and die before the end of the 12th model cycle will incur the full 12-month QALY loss, despite having died in an earlier cycle.

(g) HSCT utility decrement applied as a positive utility gain in the PSA

The deterministic version of the company's model appropriately applies a negative disutility for patients undergoing HSCT. However, the probabilistic version of the model applies this parameter as a positive utility gain. The company's probabilistic sampling procedure should have multiplied this value by -1.

As part of the clarification process, the EAG asked the company to confirm that the issues described above were errors and to rectify these issues in an updated version of the model (see clarification response,[38] questions C13-C17). Issues (e) and (g) were identified after the EAG's clarification letter was submitted. In their clarification response, the company agreed that issues (a) and (b) were minor errors. These were corrected in the company's revised model. With respect to issue (c), the company's clarification response (question C15) discusses the existing constraint which forces the cumulative probability of EFS to remain equal to or lower than the cumulative probability of OS, but does not discuss the absence of a constraint on the per-cycle EFS risk. As such, this issue remains unresolved in the company's revised model. With respect to issue (d), the company's clarification response (question C16) states that the use of unadjusted life tables in the MCM was intended and that this does not represent an error. The EAG disagrees and considers this issue to also be unresolved in the company's revised model. Regarding point (f), the company's clarification response (question C17) states that the model assumes that all patients who undergo allo-SCT survive for at least 12 months. The EAG notes that given the company's assumption that all patients survive at least 12 months following allo-SCT, it may have been simpler to apply a lump sum QALY loss to all patients in the first model cycle. The EAG also notes however that some patients may die during this initial 12-month period. These minor issues are addressed as part of the EAG's exploratory analyses (see Section 5.5).

(2) Use of data from ELIANA in preference to pooled study data from all tisagenlecleucel

The previous version of the company's model used in TA554[19] was informed by time-to-event data on EFS and OS from a pooled dataset which comprised all three tisagenlecleucel studies: ELIANA, ENSIGN and B2101J.[34-36]

NICE Guidance 554[19] highlighted that the patient population in B2101J[36] differed from the other two tisagenlecleucel studies[34, 35] in that patients had better performance status, were more likely to have undergone prior allo-SCT and could receive up to three infusions of tisagenlecleucel rather than one infusion. The TA554 guidance does not specifically state a preference for using this pooled dataset; however, the company's model based on this dataset was used for decision-making. The EAG also notes that all of the economic analyses of tisagenlecleucel included in the company's SLR of existing models included a pooled dataset including at least ELIANA and ENSIGN, and most also included B2101J (see Section 5.1).

Within the current appraisal, outcomes for the pooled dataset (N=200) are presented in the clinical section of the CS[9] as part of a meta-analysis. However, the company's economic model is based only on data from ELIANA[34] (N=79), based on the latest DCO of November 2022; data from ENSIGN and B2101J are not used in the model. This represents a substantial change from the model used to inform TA554. The company's justification for including only the data from ELIANA in the current model is given in CS Section B.3.3.1: *"The ELIANA trial is the pivotal trial that informed marketing authorisation for tisagenlecleucel in the indication of interest, has the longest follow-up and is most generalisable to the intended patient population and use of tisagenlecleucel in UK clinical practice."* Table 32 of the CS also comments that there are differences between the tisagenlecleucel studies, but does not provide further details. However, several other sections of the CS suggest the opposite position:

- Section B.2.3.2 states that *"All three trials [of tisagenlecleucel] had a very similar study design, ALL patient population and methodology."*
- *S*ection B.2.8 states *"the median dose received across all three trials was of the same magnitude and therefore this difference was not expected to bias the pooled estimate of efficacy for tisagenlecleucel."*
- Section B.2.8 concludes that *"Overall, it was considered that any differences between baseline characteristics were minor, and therefore it was considered appropriate to pool the data from all three trials [of tisagenlecleucel]. Furthermore, the eligibility criteria of all three trials match the intended patient population for tisagenlecleucel in UK clinical practice.[2, 5, 6] Therefore, taken together, the pooling of all three trials generates a larger sample size of a group of patients that can be considered, overall, to be representative of the "true" population likely to be treated with tisagenlecleucel in UK clinical practice."*

The EAG sought advice from their clinical advisors regarding whether it is appropriate to use the pooled dataset. The clinical advisors commented that the baseline characteristics for the pooled dataset are generally representative of the population of patients treated with tisagenlecleucel in the NHS. They also commented that the dose escalation approach used in Study B2101J was more likely to impact on safety rather than effectiveness outcomes; this was also the view of the company. As such, the EAG does not believe that the company's decision to exclude ENSIGN[35] and B2101J[36] from the economic analysis is appropriate, as it leads to a situation whereby relative to its entry into the CDF, uncertainty around the effects of tisagenlecleucel is reduced due to the longer follow-up in ELIANA,[34] but increased due to the exclusion of nearly two-thirds of the available outcome data on tisagenlecleucel-treated patients. Rather, the EAG believes that the tisagenlecleucel studies are sufficiently similar to warrant pooling the data from ELIANA, ENSIGN and B2101J. Using the pooled dataset increases the sample size considerably and means that all relevant evidence on the effectiveness and safety of tisagenlecleucel is included in the model, regardless of the duration of follow-up in the individual

studies. This is important because ENSIGN and B2101J reported comparatively poorer EFS and OS than ELIANA.

As part of the clarification process, the EAG asked the company for further justification regarding the exclusion of the pooled tisagenlecleucel dataset from the economic model (see clarification response,[38] question C1). In their response, the company stated: *"…when considering the data to be used in the economic model in the current submission, the use of the pooled analysis was not considered appropriate for a number of reasons: a) results of the pooled dataset versus ELIANA alone were considered to be comparable and therefore did not suggest that one dataset should be used over the other and b) use of the pooled dataset resulted in a shorter median follow-up than use of ELIANA alone (48.2 months versus 79.4 months, respectively)."* The EAG's view remains unchanged – i.e., that it is preferable to pool the data from all three tisagenlecleucel studies, as was done in TA554.[19] The revised economic model provided in the company's clarification response includes additional functionality to use parametric survival models fitted to the pooled tisagenlecleucel dataset, rather than ELIANA alone. The pooled dataset is used in the EAG's exploratory analyses (see Section 5.6).

(3) EFS definition in the tisagenlecleucel studies may exaggerate benefits

The company's model uses EFS data from ELIANA.[34] The definition of EFS in ELIANA, ENSIGN and B2101J includes censoring for allo-SCT and further anticancer therapy. The company's clarification response[38] (questions B2 and B25), states that 16 of the 18 patients who underwent subsequent allo-SCT in ELIANA had the transplant whilst in CR, and reasons for the use of allo-SCT as consolidation therapy may have included clinician judgement based on disease status (MRD positivity, B-cell recovery), or concerned parents wanting their children to receive a known curative treatment option. ELIANA did not collect data documenting the reasons for consolidation allo-SCT; the EAG presumes the same is also true of the other two tisagenlecleucel studies. The company's clarification response also states that using allo-SCT as consolidation therapy following tisagenlecleucel is no longer considered an appropriate treatment course. In their response to an additional clarification request from the EAG, the company stated that *"the inclusion of censoring for allo-SCT is more appropriate as it reflects the intended use of tisagenlecleucel as a curative treatment and averts any biases in treatment effect resultant of subsequent allo-SCT."* The EAG is unclear how many patients were censored for further therapy.

As noted in Section 4.2.2, the EAG's clinical advisors raised concerns about the definition of EFS used in the tisagenlecleucel studies,[34-36] as this includes censoring for allo-SCT and further therapy, and excludes other clinically relevant events including MRD relapse and early loss of B-cell aplasia. The advisors stated that the EFS definition and the censoring approach used in ELIANA may introduce a bias which may exaggerate the benefits of tisagenlecleucel, particularly if the indication for subsequent

allo-SCT or further therapy was the detection of MRD positivity following tisagenlecleucel, as this may indicate that the treatment has failed but this type of failure would be masked by the censoring mechanism. As noted in Section 4.2.2, a recent national UK analysis of real-world outcomes for 128 children and young adults who received tisagenlecleucel reported markedly shorter median EFS when this definition included molecular or frank relapse, further therapy, death or treatment failure (ELIANA EFS definition –22 months; stringent EFS definition –7 months).[45]

All of the parametric survival models applied in the tisagenlecleucel group of the company's model include censoring for allo-SCT and further therapy; models have not been fitted to the data without censoring. EFS for the pooled dataset with and without censoring for allo-SCT is reported in Figure 5 and Figure 6, respectively; these plots indicate that censoring allo-SCT had a limited impact on EFS. However, these analyses cannot capture the impact of including other clinically relevant events in the EFS definition such as MRD positivity. These plots also do not remove the effect of censoring for further therapy. Had a more stringent EFS definition been used, the EAG expects that this would lower the modelled tisagenlecleucel EFS function, which in turn, would reduce the mean utility gains in the first 5 years and increase the proportion of patients incurring the higher PD state follow-up costs for the tisagenlecleucel group. The impact of this issue on the ICER for tisagenlecleucel is unknown.

(4) Uncertainty relating to costs and outcomes for patients who do not receive the tisagenlecleucel infusion

The EAG has two concerns regarding the decision tree component of the company's model; these are discussed below.

(a) Assumption that patients who do not receive the infusion due to manufacturing failure or AEs accrue costs and outcomes for the comparator groups

In TA554,[19] the ERG highlighted concerns about assigning the QALYs and costs of the comparators to patients who do not receive the tisagenlecleucel infusion due to manufacturing failures or AEs. The ERG stated that in practice, these patients would likely receive palliative therapy rather than intensive therapy.

In the current appraisal, the company's model assumes that the 11.3% of patients for whom tisagenlecleucel is planned but who do not receive the infusion due to manufacturing error or progression accrue the costs and QALYs for the comparator group - 50% receive blinatumomab and 50% receive FLAG-IDA. 7.2% of patients who die prior to infusion accrue zero life years or QALYs. These assumptions are the same as those applied in the company's original model in TA554.[19]

During the clarification process for the current appraisal, the EAG requested Kaplan-Meier OS plots for patients who were enrolled into the three tisagenlecleucel studies but who did not receive the

infusion. The Kaplan-Meier plots for ELIANA[34] and ENSIGN[35] suggest very poor survival, with almost all patients dying within 6 months of study entry. Limited data are available from B2101J.[36] The Kaplan-Meier OS plot for the pooled dataset has been presented previously in Figure 10; across all non-infused patients, the restricted mean survival is less than 5 months. In contrast, the company's model suggests that patients who do not receive the infusion survive for approximately 3.9 years. This suggests that the company's model substantially overestimates the expected survival amongst patients who do not receive the infusion.

(b) Pre-treatment costs incurred in non-infused patients

In TA554,[19] the ERG report stated that the company's model likely underestimated the costs of bridging chemotherapy and lymphodepleting chemotherapy in patients who do not receive the tisagenlecleucel infusion because AEs and manufacturing failure will likely occur towards the end of the manufacturing period.

Within the current appraisal, the company's model assumes that non-infused patients incur 100% of the cost of leukapheresis, 50% of the cost of bridging chemotherapy and 50% of the cost of lymphodepleting chemotherapy. During the clarification process, the EAG asked the company to provide the number of non-infused patients in ELIANA,[34] ENSIGN[35] and B2101J[36] who received each pre-treatment component (see clarification response,[38] question B16). Based on the pooled dataset, 100% of patients received leukapheresis, 59% received bridging chemotherapy and 5.1% received lymphodepleting chemotherapy. It appears that the company's model overestimates the cost of pre-treatment in patients who do not receive the tisagenlecleucel infusion. This suggests that the model slightly overestimates the overall cost of tisagenlecleucel.

(5) Uncertainty around relative effectiveness of tisagenlecleucel versus comparators

The longer follow-up for ELIANA, ENSIGN and B2101J[34-36] has reduced uncertainty around clinical outcomes for tisagenlecleucel. However, as discussed in Chapter 4, the relative effectiveness of tisagenlecleucel versus blinatumomab and salvage chemotherapy remains highly uncertain and difficult to quantify due to the following factors:

- There are no RCTs comparing tisagenlecleucel versus any other comparator in the relevant R/R B-cell ALL population. The available evidence for tisagenlecleucel and its comparators is limited to single-arm studies.
- The EAG's clinical advisors commented that the proportion of patients receiving allo-SCT and the resulting survival curves reported in von Stackelberg *et al.*[15] and Jeha *et al.*[14] are lower than would be expected in NHS practice for patients receiving blinatumomab and FLAG-IDA.
- As noted in Section 4.1, the EAG has concerns regarding the lack of transparency around the selection of comparator studies for inclusion in the company's ITCs (von Stackelberg *et al.*[15]

and Jeha *et al.*[14]). The EAG considers that there are other potentially more relevant studies which should be considered in the economic analyses (in particular, RIALTO[16] and Kuhlen *et al.*[52]).

- The single-arm design of the studies of tisagenlecleucel, blinatumomab and salvage chemotherapy means that only unanchored ITCs can be performed. Unanchored ITCs are at high risk of bias and confounding.[61]
- The company has undertaken unanchored MAICs of tisagenlecleucel versus blinatumomab and salvage chemotherapy. These analyses assume that all potential prognostic factors and treatment effect modifiers have been included in the adjustment model. This is a very strong assumption which is generally considered impossible to meet.[61] As shown in Section 4.9, the MAIC-adjusted OS is very similar to unadjusted OS.
- The company's base case analyses are based on naïve ITCs. These analyses assume that the distributions of all prognostic factors and treatment effect modifiers are equivalent between the studies. This is also a very strong assumption which is unlikely to be appropriate.

The EAG considers these issues to be unresolvable given current evidence and therefore the results of the company's model and the EAG's exploratory analyses should be interpreted with caution.

(6) Issues relating to the company's survival analysis

In TA554,[19] the ERG highlighted uncertainty around the long-term benefits of tisagenlecleucel on EFS and OS, in particular, whether tisagenlecleucel can be considered to be a curative treatment. In this earlier appraisal, the company fitted a range of standard parametric models, MCMs and restricted cubic spline (RCS) models to the available data for tisagenlecleucel and its comparators. The company's MCMs reportedly produced a wide range of cure fractions for the tisagenlecleucel group, although these were redacted from the committee papers. NICE Guidance 554 concluded that due to the short follow-up in the tisagenlecleucel studies (median follow-up of <3 years in each study at the time of TA554) there was no robust evidence that tisagenlecleucel has a curative effect.[19]

A key difference between TA554 and the current appraisal is that longer-term follow-up data are now available for all three tisagenlecleucel studies. Despite the availability of this longer-term evidence, the EAG has several concerns regarding the company's survival analysis presented in the CS.[9] These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[85, 86]

(a) Use of independent versus jointly fitted models

As ELIANA,[34] von Stackelberg *et al.*[15] and Jeha *et al.*[14] are all single-arm studies, the company had no option other than to fit models independently to each treatment group. The EAG considers this aspect of the company's survival modelling approach to be appropriate.

(b) Range of models assessed

As noted in Section 5.2.4, within the current appraisal, the company fitted standard parametric models and MCMs to the available data for tisagenlecleucel and its comparators. In contrast to the analyses conducted to inform TA554,[19] the company did not fit RCS models to the data within the current appraisal. The company discounted all of the standard parametric models because they did not provide a good representation of the observed OS and EFS data (see Figure 21, Figure 23 and Figure 25). All of the survivor functions included in the company's base case analysis are MCMs. The EAG's clinical advisors commented that they believe that tisagenlecleucel (without subsequent allo-SCT) and blinatumomab/FLAG-IDA followed by allo-SCT are each expected to be curative in some patients; hence, the use of MCMs is reasonable in principle. However, NICE TSD21 highlights that the reliability of MCMs is dependent on there being sufficient follow-up and numbers of events. As noted by the ERG in TA554, both of the comparator studies were subject to short follow-up periods (around 2 years in von Stackelberg *et al.*[15] and 90 weeks in Jeha *et al.*[14]). The EAG is unsure about the reliability of the MCM parameters estimated from these studies.

The EAG believes that the use of more flexible parametric survival models may have been better able to reflect the shape of the underlying hazards in the observed data and could have been combined with a structural assumption of a cure timepoint. This would have provided an alternative approach for modelling clinical outcomes, including cure. The EAG notes that most of the previous economic analyses included in the company's SLR included this type of approach (see Section 5.1).

(c) Statistical and visual goodness-of-fit

The company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The EAG notes the following for each endpoint and each treatment group:

- *Tisagenlecleucel OS* (Table 31 and Figure 22). The company selected the log-logistic MCM for inclusion in the base case analysis. This distribution is the second best-fitting MCM based on AIC and BIC. The log-logistic model provides a generally reasonable visual fit to the observed data, although all of the MCMs for OS provide similar model predictions over the observed period of ELIANA.[34]
- *Tisagenlecleucel EFS* (Table 38 and Figure 28). The company selected the log-logistic MCM for inclusion in the base case analysis. This distribution is the best-fitting MCM according to AIC and the second best-fitting MCM according to BIC. The log-logistic model provides a generally reasonable visual fit to the observed data from ELIANA but appears to underestimate EFS after around 18 months. All of the MCMs provide similar estimates of EFS over the observed period of ELIANA.[34]
- *Blinatumomab OS* (Table 34 and Figure 24). The company selected the log-normal MCM for inclusion in the base case analysis. This distribution is the best-fitting MCM according to AIC

and the second best-fitting model according to BIC. The log-normal distribution provides good visual fit to the observed data. All of the fitted MCMs suggest similar predictions within the observed period of the von Stackelberg *et al.* study.[15]

- *FLAG-IDA OS* (Table 36 and Figure 26). The company selected the log-normal MCM for inclusion in the base case analysis. This distribution is the best-fitting MCM according to both AIC and BIC. The model provides a good visual fit to the observed data, although all MCMs suggest a similar OS projection within the observed period of the Jeha *et al.* study.[14]

(d) Consideration of nature of hazards

The CS[9] does not provide plots of the empirical or modelled hazards for EFS or OS. Following a request for additional analyses from the EAG (see clarification response,[38] question C3), the company provided plots of the empirical smoothed hazard from the pooled dataset for EFS and OS (see Figure 34 and Figure 35, respectively). These plots suggests that within the overall population, the hazard of death increased initially and then dropped substantially, with the hazard subsequently slowing over time. This pattern is broadly consistent with the hazard function for the log-logistic MCM EFS and OS functions applied in the company's base case model (see Figure 36).

Figure 34: Empirical/smoothed hazard function for EFS from the pooled dataset (reproduced from clarification response, question C3, Figure 14)

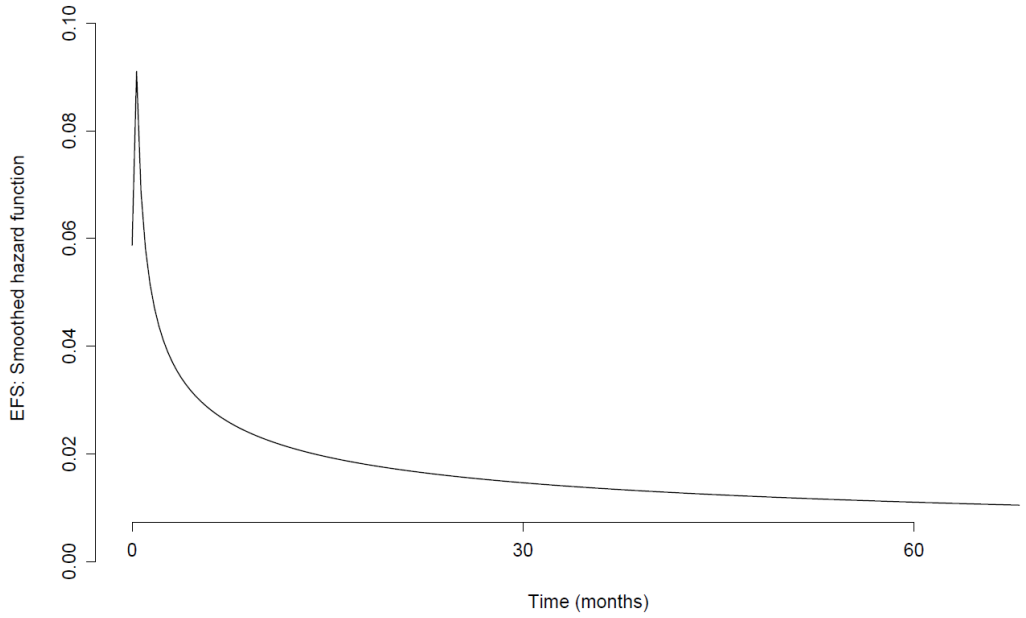


Figure 35: Empirical/smoothed hazard function for OS from the pooled dataset (reproduced from clarification response, question C3, Figure 14)

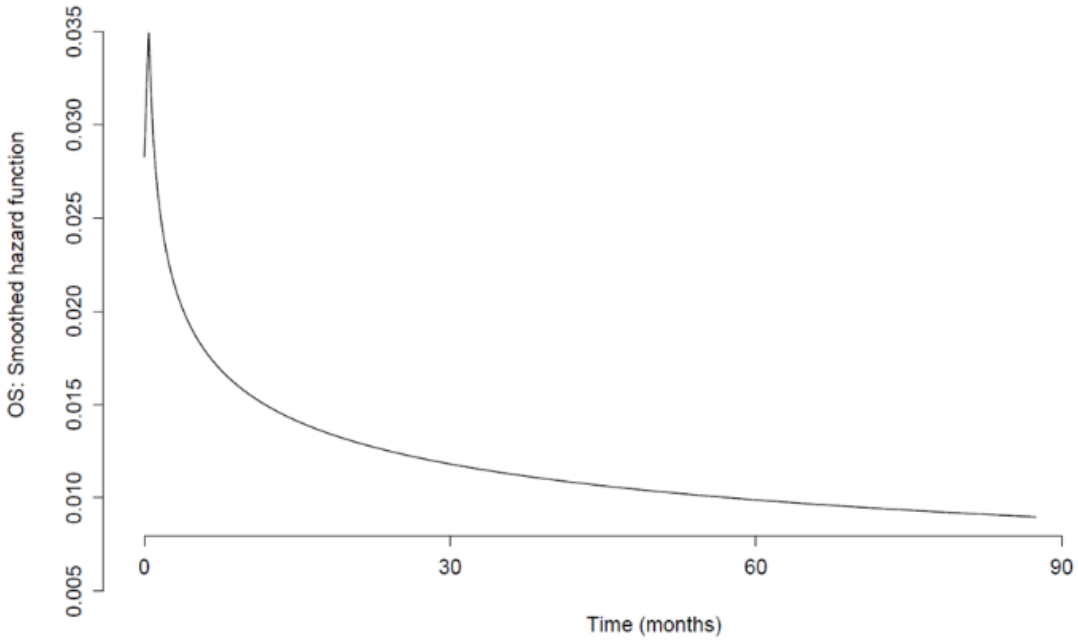
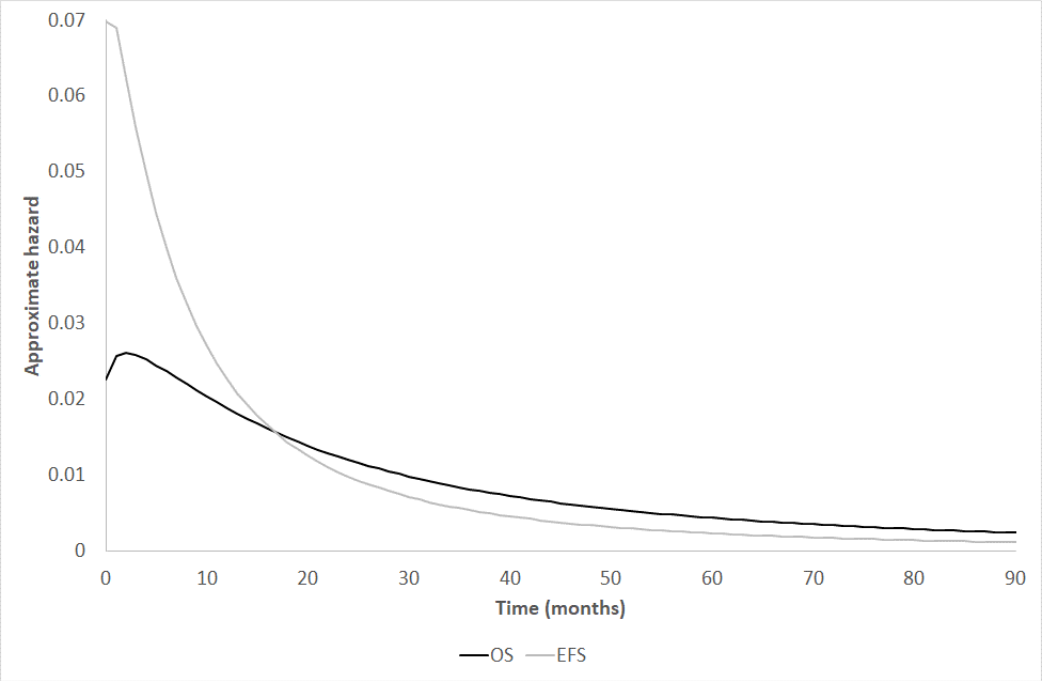


Figure 36: Modelled hazard for EFS and OS based on the overall model trace for the pooled dataset (including cured and non-cured patients)



(e) Consideration of long-term clinical plausibility and cure assumption

The CS[9] contains useful information on the range of expectations of OS and EFS provided by the clinical experts consulted by the company. Further information on the clinical experts' views was also provided as part of a 2023 clinical validation report.[27] The EAG notes three limitations which are discussed below.

(i) Clinical validation exercise limited to the ELIANA data

The company's clinical validation report[27] indicates that the participating clinical experts were shown Kaplan-Meier plots from the latest DCO of ELIANA[34] and predictions from survival models fitted to these data. As noted in critical appraisal point (2), the EAG believes that the pooled dataset should be used as the basis for the economic model. It is unclear whether the clinical experts' expectations of long-term EFS and OS for tisagenlecleucel would differ had the company presented them with the observed pooled data and survival models fitted to the pooled dataset.

(ii) Selection of the log-logistic mixture cure model for OS in the tisagenlecleucel group

The company's preferred model for OS in the tisagenlecleucel group is the log-logistic MCM (fitted to ELIANA only, rather than the pooled dataset). However, the log-normal MCM is more closely aligned with the clinicians' estimates than the log-logistic MCM at every time point. The log-normal MCM suggests a comparatively lower cure fraction than the log-logistic MCM. During the clarification process, the EAG asked the company why they had selected the log-logistic MCM in preference to the log-normal MCM (see clarification response,[38] question C6). In their response, the company stated that: *"the log-normal model's predicted cure fraction (32.8%) is poorly aligned with clinicians' predictions (40.0%), as compared with the cure fraction predicted by the log-logistic model (42.4%). Furthermore, the log-logistic and exponential model curves were explicitly noted by clinicians as most closely aligning with their expectations of tisagenlecleucel efficacy in terms of OS. The log-normal model is therefore likely to underestimate long-term ALL survivorship, and was therefore not considered appropriate for inclusion in the Company base case, in favour of the log-logistic model. The exponential model was used in a scenario analysis."*

Had it been reasonable to focus on ELIANA[34] only, the EAG believes that the company should have selected the log-normal MCM as this aligns with the experts' expectations of OS. For MCMs estimating OS, the cumulative OS probability at any timepoint is determined as a function of the cure fraction, and the hazards of death in each of the non-cured and cured subgroups. Eliciting a cure fraction from clinical experts may not be particularly meaningful – the cure fraction is a statistical concept, whereby the survivor function of the MCM asymptotes to the cure fraction at time infinity.[86] The EAG believes it is unlikely that this is how the company's clinical experts expressed expectations of cure and therefore it is probably more reasonable to rely on the clinical experts' expectations of cumulative OS at specific timepoints. Despite this criticism, as noted above, the EAG believes that the economic model should be based on the pooled tisagenlecleucel dataset.

(iii) Reliance on the cure fraction to justify selection of OS models for blinatumomab and FLAG-IDA

Whilst the company's clinical validation report[27] states that the company elicited expectations of EFS and OS for tisagenlecleucel, blinatumomab and FLAG-IDA from their clinical experts, it appears that

this exercise was limited only to tisagenlecleucel as no estimates are presented for the comparators. The justification for the company's selected OS models for blinatumomab and FLAG-IDA provided in the CS[9] is based on statistical goodness-of-fit and by estimating the predicted proportion of cured patients (assuming that 40% of those bridging to allo-SCT will achieve cure), and comparing this to the cure fraction estimated by the MCMs. The EAG would have preferred that the company had elicited EFS and OS estimates for all treatments, or at least shown the experts the modelled survival functions, as was done for the tisagenlecleucel group. The EAG's clinical advisors indicated that they would expect roughly half of blinatumomab-treated patients who proceed to allo-SCT to achieve cure; this would indicate that OS is likely to have been underestimated for the comparators, particularly in the blinatumomab group.

(f) Sensitivity analysis conducted by the company

The CS[9] includes three sensitivity analyses around the choice of parametric survival functions (see Table 49, Scenarios SA1, SA2 and SA3). The EAG considers this range of scenarios to be limited and believes that other MCMs for EFS and OS, as well as model forms (e.g., RCS models), should have been considered. As such, the uncertainty around the relative effectiveness of tisagenlecleucel versus its comparators appears to have been under-represented in the CS.

Conclusions on the company's survival analysis

Overall, the EAG considers the company's survival analysis to be generally reasonable with respect to the analyses presented, but highlights the following points:

(i) The standard parametric survival models do not provide a good representation of the observed data. The only other type of models considered are MCMs. This means that all of the survival models included in the company's economic model are reliant on there being sufficient follow-up and numbers of events to estimate a reliable cure fraction. This may not be the case, particularly for the studies reported by Jeha *et al.*[14] and von Stackelberg *et al.*[15] The EAG believes it would have been prudent to explore the use of other flexible parametric models, including the structural assumption of a cure timepoint.

(ii) For the ELIANA data only, the EAG prefers the use of the log-normal MCM rather than the log-logistic MCM for OS in the tisagenlecleucel group because it is more closely aligned with the company's experts' expectations of OS at every time point. The EAG does not consider reliance on elicited cure fractions to select preferred survival models to be an optimal approach.

(iii) The EAG believes that OS in the comparator groups is likely to have been underestimated.

(7) Uncertainty around excess mortality risks in cured patients

The company's model assumes that patients who are cured are subject to an excess risk of mortality relative to the general population, based on an SMR of 4.0. This was based on the mean of the most

likely SMRs obtained from clinical experts consulted by the company.[27] This value is considerably lower than the SMR applied in the TA554 model (previous SMR of 9.05, based on MacArthur *et al.*[87]). The company's clarification response[38] (question C5) states that since TA554, clinicians have gained more experience of using CAR-Ts and highlights that lower SMRs have been applied in other more recent appraisals of CAR-Ts (including brexucabtagene for R/R B-cell ALL, TA893[22]). The EAG notes that the clinical experts consulted by the company provided a wide range of lower and upper plausible SMRs of 1.5 and 10, although their "most likely" estimates suggested a narrower range of 3.0 to 4.0. Overall, the EAG considers that the true SMR for patients who are long-term survivors following tisagenlecleucel remains uncertain.

(8) Issues relating to the utility and disutility values applied in the company's model

The utility values and related assumptions applied in the company's base case model are similar to those applied in the previous model used to inform TA554.[19] In this earlier appraisal, the ERG raised several concerns, including: (i) the use of utility values for the EF and PD health states from Kelly *et al*.[73] which are higher than those estimated using ELIANA data;[34] (ii) uncertainty around the assumption that long-term survivors/cured patients will experience a level of HRQoL equivalent to the EF state; (iii) the omission of disutility values related to lower grade CRS and other Grade <3 AEs; (iv) the exclusion of AE events that occurred beyond 8 weeks of tisagenlecleucel infusion, and (v) not considering improvements in HRQoL over time following allo-SCT. Several of these criticisms also apply to the company's model for the current appraisal. Specific concerns regarding the individual parameter values are summarised below.

EFS and PD utility values

NICE Guidance 554[19] comments that the structural assumption of improved HRQoL for long-term survivors after 5 years was appropriate. The guidance document does not comment on the appropriateness of the sources of the health state utility values.

As part of the current CS, the company undertook an SLR of HRQoL studies to inform the economic model (CS Appendix H[39]). The company prioritised only two studies for inclusion in the review: (i) Aristides *et al.*[88] and (ii) NOMA.[70] Aristides *et al.* is a time trade-off (TTO) study which reports utility values for five health states associated with R/R B-precursor ALL. NOMA is the Norwegian Single Technology Appraisal (STA) previously described in the company's SLR of existing economic analyses (see Section 5.1, Table 28); this report includes utility values based on EQ-5D-3L data from ELIANA.[34] The company chose not to use estimates from Aristides *et al.* in the model because paediatric patients were not included and data were not presented separately for young adult patients. The company chose not to use the EQ-5D-3L estimates from ELIANA (used in the NOMA appraisal) in the base case analysis due to the limited sample size.

The company's base case model applies utility values of 0.91 and 0.75 for the EF and PD states, respectively, based on Kelly *et al*.[89] After 5 years, the utility value for surviving patients in both states is assumed to be the same as that for the EF state (utility=0.91). The CS[9] also presents a sensitivity analysis in which it is stated that the utility values from ELIANA[34] are used for the first 2 years followed by Kelly *et al.* (see Table 49, Scenario SA5); however, the EAG notes that the executable model applies the utility values from ELIANA for 2 years, with the long-term survivor utility value also based on ELIANA.

The EAG has summarised the health state utility values used in existing economic analyses of tisagenlecleucel included in the company's SLR (see Table 52). Each of these previous models have either used Kelly *et al.*[89] or the ELIANA[34] as the source of the utility values, together with an assumption about HRQoL for long-term survivors after a particular timepoint (where reported). The EAG considers the company's analyses around health state utility values to be consistent with previous models and notes that neither source is ideal.

Table 52: Utility values applied in previous economic models of tisagenlecleucel included in the company's SLR, the TA554 model and the company's current model

Study	EF utility	PD utility	Long-term survivor utility	Sources
Carey *et al.* (2022)[65]	EQ-5D-3L 0.80	EQ-5D-3L 0.63	EFS value after 60 months 0.80	ELIANA[34]
Moradi-Lakeh *et al.* (2021)[67]	SF-36 value mapped to HUI-2. 0.91	CHRI mapped to EQ-5D. 0.75	Not reported	Kelly *et al.*[89] (Values not reported.)
Thielen *et al.* (2020)[68]	EQ-5D-3L 0.83	EQ-5D-3L 0.68	Not reported	ELIANA[34] (Dutch tariff)
Ribera Santasusana *et al.* (2020)[66]	SF-36 value mapped to HUI-2. 0.91	CHRIs mapped to EQ-5D. 0.75	Not reported	Kelly *et al.*[89]
NoMA (2018)[70]	EQ-5D-3L 0.80	EQ-5D-3L 0.63	EF value after 5 years	EF and PD utility from ELIANA.[34] Long-term survivor utility from Kelly *et al*.[89]
TA554 (2018)[19]	SF-36 value mapped to HUI-2. 0.91	CHRIs mapped to EQ-5D. 0.75	EF value after 5 years 0.91	Kelly *et al.*[89]
Current model (2023)[9]	SF-36 value mapped to HUI-2. 0.91	CHRIs mapped to EQ-5D. 0.75	EF value after 5 years 0.91	Kelly *et al.*[89]

EF - event-free; PD - progressed disease; EQ-5D-3L - Euroqol 5-Dimensions 3-Level; HUI-2 - Health Utilities Index Mark 2; CHRI - Child Health Rating Inventory; SF-36 - Short Form 36; NoMA - Norwegian Medicines Agency

Disutility values related to AEs, ICU stays due to CRS and ICU stays due to other non-CRS events

The TA554 Guidance document[19] does not comment on the company's assumptions regarding the disutility associated with AEs. In the current appraisal, the company's model assumes a disutility value of -0.42 for the mean duration of hospitalisation for each treatment. The EAG is unclear whether it is reasonable to assume that a disutility should only apply to days spent in hospital, as some AEs may persist for a longer duration. Nonetheless, this is not a key driver of the ICER and the approach is consistent with that used in TA554.

The EAG believes that the company's assumption that ICU stays for CRS and non-CRS events are associated with a utility value of zero seems reasonable. These values are not key drivers of the ICER.

HRQoL improvement over time post allo-SCT

In TA554,[19] the company assumed that allo-SCT was associated with a utility decrement of -0.57 for a period of 1 year, based on Sung *et al.*[74] In this earlier appraisal, the ERG raised concerns that the duration of SCT-related disutility may be overestimated. The NICE Guidance document does not comment on these assumptions; however, NHSE agreed that the assumed duration for which the disutility was applied was excessive given the age of the target population. Within the current appraisal, the company has applied the same assumptions as those used in TA554. The company has also explored a scenario in which a lower disutility of -0.13 is applied, based on Felder-Puig *et al.*[90] (see Table 49, Scenario SA6). The EAG notes that this is not a key model driver.

(9) Issues relating to costs (excluding the pre-treatment phase)

In TA554,[19] the ERG raised several concerns regarding the resource use and cost estimates applied in the company's earlier model. These included concerns about: (i) the exclusion of training costs for health care professionals delivering tisagenlecleucel; (ii) the overestimation of the costs of blinatumomab treatment; (iii) uncertainty around the expected costs of allo-SCT in each treatment group; (iv) the potential underestimation of the costs of managing CRS in ICU; (v) uncertainty around the proportion of patients requiring IVIg treatment for B-cell aplasia and the duration for which treatment would be required and (vi) the costs of terminal care.

As noted in Section 5.2.4, since TA554, NHSE has constructed a tariff for the delivery and follow-up of CAR-T therapies which includes the costs of leukapheresis, delivery of the CAR-T in hospital, AEs occurring in hospital, monitoring for 100 days and training.[22] This tariff cost is included in the company's base case model for the current appraisal. As such, the ERG's concerns regarding issues (i) and (iv) can be considered to have been resolved. According to NICE Guidance 554,[19] the Appraisal Committee concluded that it is appropriate to assume that patients would receive 2 cycles of blinatumomab (issue (ii) above). The company's current model assumes that patients receive up to 2

cycles of blinatumomab and is therefore in line with the Appraisal Committee's previous preferred assumption. The EAG's clinical advisors confirmed that this treatment duration is appropriate. The EAG believes that issues (iii), (v) and (vi) remain subject to uncertainty – these issues are discussed below.

Cost of allo-SCT

In TA554,[19] the ERG commented that the company's model used allo-SCT rates for FLAG-IDA and blinatumomab from comparator studies which may not reflect patients who would be eligible for treatment with tisagenlecleucel. In this previous appraisal, the ERG also commented that the source of post-transplant follow-up costs is very old (van Agthoven *et al.*, 2002[91]) and that these SCT costs may not reflect current practice. NICE Guidance 554[19] highlighted uncertainty around the sources of data used to inform outcomes for the comparators and reported estimated rates of allo-SCT provided by NHSE of 15-20% for salvage chemotherapy and at least 24% for blinatumomab.

Within the current appraisal, the company has used the same approach as in TA554, with allo-SCT rates based on von Stackelberg *et al.*[15] and Jeha *et al.*,[14] and post-transplant follow-up costs based on van Agthoven *et al.*,[91] uplifted to current prices. As with the model used in TA554, the rate of allo-SCT following FLAG-IDA is assumed 14.8%, which is towards the lower end suggested by NHSE in TA554, and is lower than the rates suggested by clinical advisors to the company and the EAG (25% or higher). The rate of allo-SCT following blinatumomab is assumed to be 34.3% which is substantially higher than the rate suggested by NHSE in TA554, but lower than the rates suggested by clinical advisors to the company and the EAG (50% or higher). Unit costs for stem cell harvesting and the transplant procedure have been updated using current NHS Reference Costs.[77] The EAG believes that there remains uncertainty around the costs of allo-SCT for each treatment group in the model.

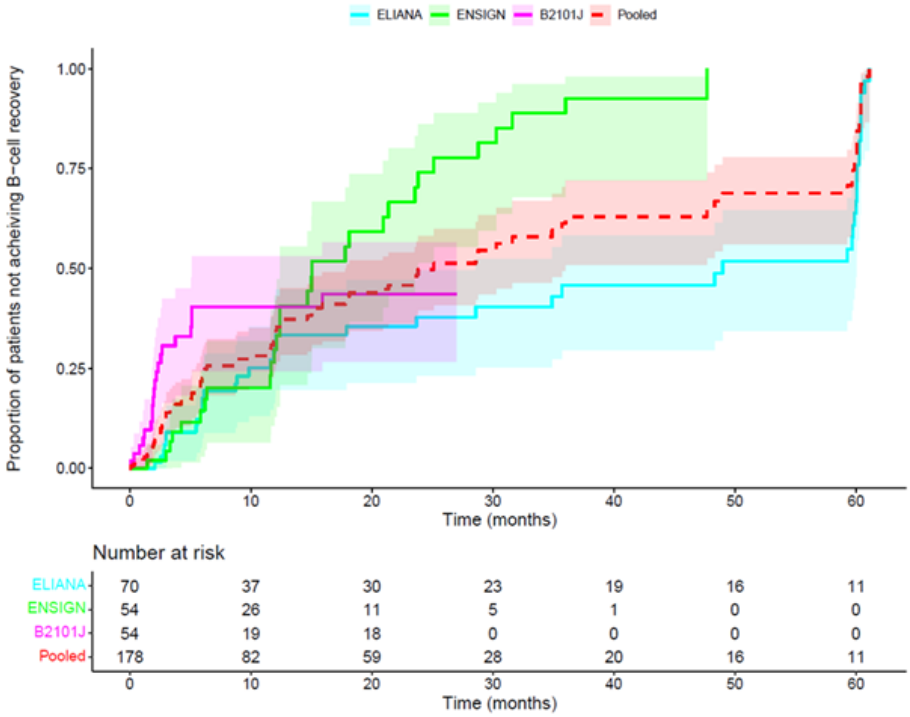
Costs of treating B-cell aplasia

In TA554,[19] the ERG noted that there was uncertainty around the time to B-cell recovery following the tisagenlecleucel infusion and commented that the company's use of the median duration is likely to underestimate the mean duration, thereby underestimating expected costs. The ERG also raised concerns that the company may have overestimated the proportion of patients who will receive IVIg. NICE Guidance TA554[19] commented that long-term treatment with IVIg would only be considered for patients with concurrent infections, and stated that there were insufficient data on the rate of infections to determine how often long-term treatment is required. The Appraisal Committee concluded that that it was unknown how many patients would need IVIg treatment for B-cell aplasia and for how long treatment would be required.

In the current appraisal, the company's original model assumed that 73.33% of patients receiving tisagenlecleucel will experience hypogammaglobulinemia, of whom 75% will require IVIg replacement therapy for a duration of 11.4 months, resulting in an expected cost of £11,177 for IVIg per patient receiving the tisagenlecleucel infusion. At the clarification stage, the company stated that the value of 73.33% should instead have been reported as 40.5%; this correction was included in the company's revised model (see Section 5.4).

During the clarification round, the EAG asked the company to provide updated estimates of the time to B-cell recovery in ELIANA,[34] ENSIGN,[35] B2101J[36] and the pooled dataset (see clarification response,[38] question C11). This plot is shown in Figure 37. The EAG notes that based on this plot, the restricted mean time to B-cell recovery for the pooled dataset is approximately 30 months; this is substantially longer than the duration assumed in the company's base case (11.4 months). The EAG also notes that the median time to B-cell recovery in the latest data-cut of ELIANA is also much longer than the duration applied in the company's model.

Figure 37: Time to B-cell recovery (reproduced from clarification response, question C11, Figure 16)



The EAG asked the company to clarify why the estimate of IVIg treatment duration used in the model was shorter than that reported in ELIANA.[34] In their response, the company stated that two of the three clinical advisors consulted by the company had commented that the median time to B-cell recovery in ELIANA was an overestimate (reported in the ELIANA CSR to be 38.6 months) but that they could not comment on an alternative duration.[27] As such, the model retains the estimate of 11.40 months from the company's earlier model for TA554.[19] The EAG notes that the estimated duration of 11.40 months

reflects an earlier data-cut of ELIANA[34] and is therefore somewhat arbitrary given that the clinical outcomes data used in the model reflect a later data-cut.

Towards the end of the assessment period, NHSE provided additional information on IVIg treatment duration from the SACT dataset.[37] Amongst 121 patients who received the tisagenlecleucel infusion, 57 patients (47.1%) received IVIg treatment. The NHSE report states that the mean time to discontinuation of IVIg was 13.3 months. The EAG believes that this value reflects a crude mean of event and censoring times, which will be downwardly biased. Given that the data are time-to-event in nature, the mean should be estimated as the area under the curve (AUC). The area under the Kaplan-Meier curve for time to treatment discontinuation for these 57 patients suggests a mean IVIg duration of approximately 18 months. These data therefore suggest that the company's model underestimates both the proportion of patients requiring IVIg replacement therapy and the duration over which treatment is required. Exploratory analyses applying longer durations of IVIg treatment are presented in Section 5.5.

One of the EAG's clinical advisors commented that some patients may be able to receive subcutaneous immunoglobulin (SCIg) rather than IVIg, thereby avoiding the need to attend hospital for treatment. This may lead to a reduction in administration costs for patients requiring IVIg, although this potential saving would not apply to all patients requiring immunoglobulin replacement therapy. The magnitude of these potential savings is not fully clear and is not assessed in the EAG's exploratory analyses.

Costs of terminal care

In TA554,[19] the ERG noted that terminal care costs were not applied to patients who die before receiving the tisagenlecleucel infusion. The ERG commented that it was unclear whether this omission was intentional. NICE Guidance 554[19] does not comment on this issue.

The EAG notes that the same issue applies in the company's model for the current appraisal. The EAG believes that terminal care costs should be included for patients who die prior to receiving the infusion.

5.4 Summary of company's revised model

As part of their response to clarification questions from the EAG, the company provided two updated versions of the model. The latest version of the model included the following amendments:

- The correction of two minor model errors (see Section 5.3.5, critical appraisal points 1a and 1b)
- An updated estimate of the proportion of patients with hypogammaglobulinemia (40.5% rather than 73.3%).
- Additional functionality to model EFS and OS for tisagenlecleucel using the pooled dataset rather than ELIANA alone
- Updated EFS and OS coefficients
- Additional functionality to model OS for tisagenlecleucel using the MAIC-adjusted functions

- Additional functionality to estimate AEs using the pooled dataset
- Additional functionality to model EFS and OS for FLAG-IDA using Kuhlen *et al*.[52] rather than Jeha *et al.*[14]

Based on this updated model, the company's deterministic base case ICER for tisagenlecleucel versus blinatumomab was reduced from £19,218 to £18,554 per QALY gained, whereas the deterministic base case ICER for tisagenlecleucel versus FLAG-IDA was reduced from £30,778 to £30,202 per QALY gained.

5.5 Exploratory analyses undertaken by the EAG - methods

The EAG undertook exploratory analyses (EAs) using the second updated model provided in the company's clarification response.[38] All EAs were undertaken using the deterministic version of the model. Probabilistic ICERs were also generated for the EAG's preferred analysis (EA7b). All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the PAS price of tisagenlecleucel and exclude QALY weighting, unless otherwise stated. The results of the analyses including price discounts for comparator therapies are provided in a separate appendix to this report.

EAG's preferred analysis

The EAG's preferred analysis is comprised of six sets of amendments to the company's revised model. Each of EAs1-6 are applied incrementally.

EA1: Correction of errors

The following corrections were applied to the company's model:

EA1a: General population mortality was modelled using a weighted survival model. This change was included using a pre-existing menu in the company's revised model.

EA1b: Per-cycle general population mortality risks were applied for 12 monthly cycles. This change was also included using a pre-existing menu in the company's revised model.

EA1c: The per-cycle risk of dying due to any cause (including the SMR) was applied as a constraint to the EFS function.

EA1d: The SMR-uplifted general population mortality risks were applied as an OS constraint for non-cured patients and were used to characterise mortality risk for cured patients in the MCM.

EA1e: The model was amended to use life tables for England only.

EA1g: The sampled HSCT disutility value was multiplied by minus one.

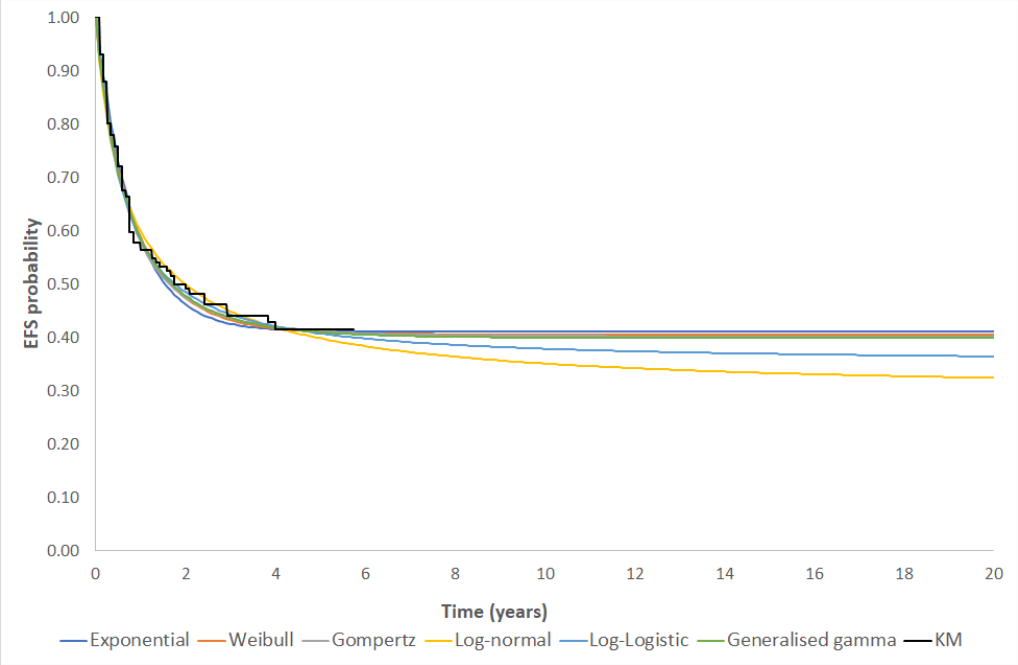
Critical appraisal point 1f, which relates to the disutility for allo-SCT being unrelated to the model trace, was not amended as this issue is minor.

These model corrections are included in all subsequent exploratory analyses.

EA2: Use of the pooled tisagenlecleucel dataset

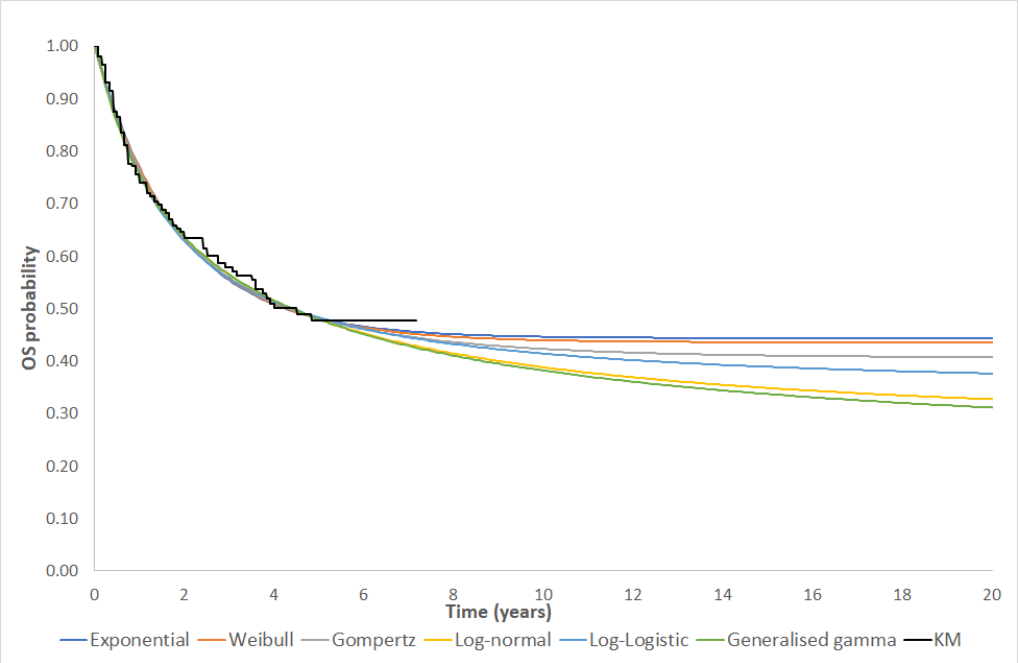
The company's revised model includes parametric survival models fitted to data on EFS (Figure 38) and OS (Figure 39) from the pooled tisagenlecleucel dataset. The EAG selected preferred parametric survival models for EFS and OS based on consideration of statistical goodness-of-fit, consideration of the hazards, visual inspection and clinical plausibility (based on input from two of the EAG's clinical advisors). Consideration was given only to MCMs.

Figure 38: Tisagenlecleucel, pooled dataset, EFS (including censoring for allo-SCT), MCMs



Survival models exclude general population mortality risks

Figure 39: Tisagenlecleucel, pooled dataset, OS, MCMs



Survival models exclude general population mortality risks

For EFS, the EAG's first clinical advisor did not consider the log-normal or log-logistic MCMs to be clinically plausible, and so these models were not considered further by the EAG. The remaining models are visually very similar, although the exponential model does not appear to represent the EFS function as well as the Weibull, Gompertz and generalised gamma MCMs. The EAG selected the Gompertz MCM for inclusion in its preferred analysis as this is the best-fitting of these models, based on AIC and BIC. The EAG's second clinical advisor agreed that the more favourable MCMs were plausible.

For OS, the EAG's first clinical advisor considered the log-logistic MCM to be clinically plausible; this is the same function applied in the company's base case model (albeit fitted to ELIANA data only). This is the second best-fitting model according to AIC and the third best-fitting model according to BIC. This model was included in the EAG's preferred analysis. The EAG's second clinical advisor preferred the more optimistic exponential and Weibull MCMs; the EAG explored the use of these more optimistic MCMs separately in additional sensitivity analyses.

These amendments were implemented using pre-existing menus in the company's revised model.

Within this analysis, the EAG also amended the allo-SCT rate and AE frequencies to reflect the pooled tisagenlecleucel dataset. This analysis therefore applies a pooled allo-SCT rate of 17.5%.

EA3: Alternative comparator studies and models

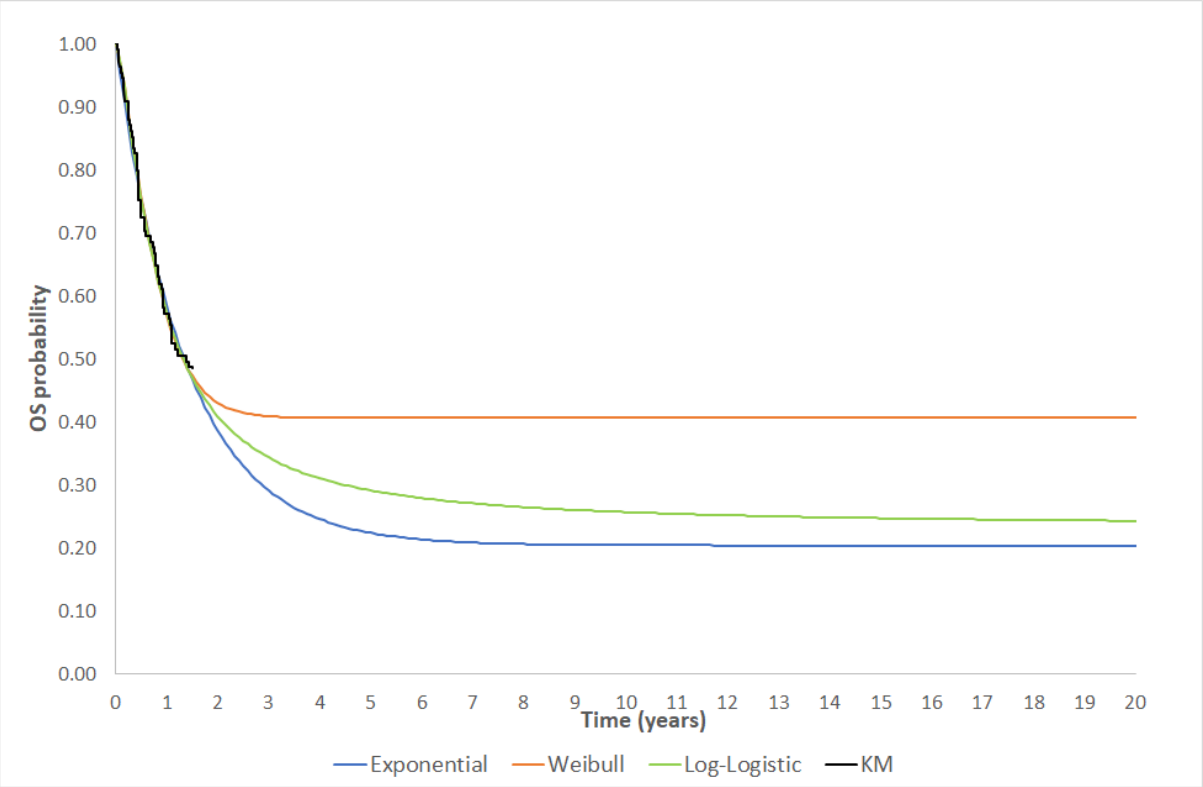
Alternative comparator study for blinatumomab

The EAG's clinical advisors commented that the proportion of patients proceeding to allo-SCT in von Stackelberg *et al.*[15] and the OS outcomes reported from this study, are lower than would be expected in the tisagenlecleucel-eligible population. The clinical advisors considered that the allo-SCT rate and the OS outcomes reported in the RIALTO study[47] are likely to be more representative of what might be expected within the target population for tisagenlecleucel; within this study, 53% of patients went on to receive subsequent allo-SCT following treatment with blinatumomab. This exploratory analysis includes RIALTO instead of von Stackelberg *et al.* The EAG also considered including the NEUF study[49] as the source of comparator data; however, this was rejected as only 26% of patients in this study underwent allo-SCT; this rate is lower than would be expected in clinical practice.

The EAG digitised the OS data from the publication of RIALTO,[47] generated pseudo-IPD using the algorithm reported by Guyot *et al.*,[81] and fitted MCMs to the replicated OS data. The MCMs were fitted using the R package *flexsurvcure*. The authors of this package warn that the generalised gamma, generalised F and Gompertz distributions have issues with convergence and numerical instability and so these models were not considered. The log-normal MCM was fitted but was subject to apparent estimation errors. As such, the EAG focussed on the exponential, Weibull and log-logistic MCMs. There was very little difference in AIC and BIC between these models. Based on clinical opinion, the

EAG selected the log-logistic MCM to represent OS for blinatumomab. An additional sensitivity analysis was conducted using the less optimistic exponential MCM.

Figure 40: Blinatumomab, RIALTO, OS, MCMs

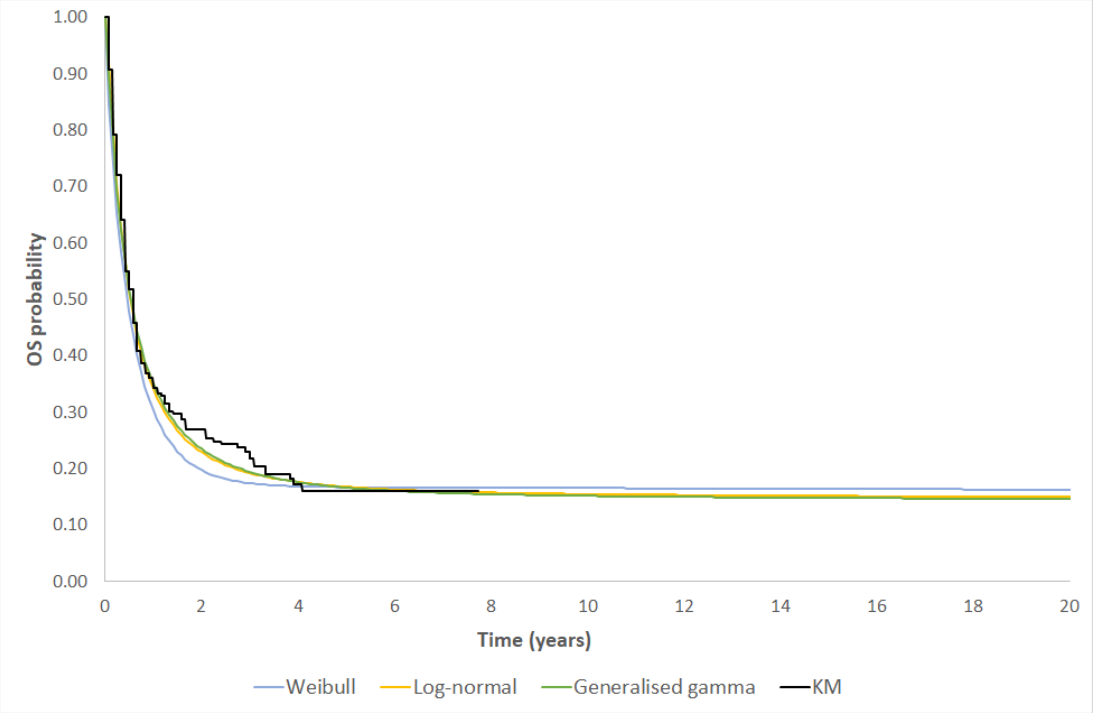


Survival models exclude general population mortality risks

Alternative comparator study for FLAG-IDA

For the FLAG-IDA group, one of the EAG's clinical advisors believed that the study reported by Kuhlen *et al.*[52] may be more representative of outcomes for patients receiving salvage chemotherapy than Jeha *et al.*[14] This exploratory analysis therefore includes Kuhlen *et al.* as the source of outcomes data for FLAG-IDA. The company included the parameters of MCMs fitted to the Kuhlen *et al.* OS data in the revised model provided as part of their response to clarification questions. The company's revised model included Weibull, log-normal and generalised gamma MCMs. The log-normal MCM was the best-fitting model based on both the AIC and BIC. The EAG selected the log-normal MCM for inclusion in the preferred analysis. As the company did not provide the covariance matrix for the models fitted to the Kuhlen data, the EAG digitised the published Kaplan-Meier OS plot, generated pseudo-IPD and re-fitted the log-normal distribution. The cure fraction obtained from this analysis was very similar to that provided by the company. The updated log-normal MCM parameters and the associated covariance matrix are used in the EAG's analysis. The EAG's second clinical advisor thought that OS for patients receiving FLAG-IDA would likely lie between the reported OS functions in Kuhlen *et al.* and Jeha *et al.* This scenario is tested as an additional sensitivity analysis.

Figure 41: FLAG-IDA, Kuhlen *et al.*, OS, MCMs

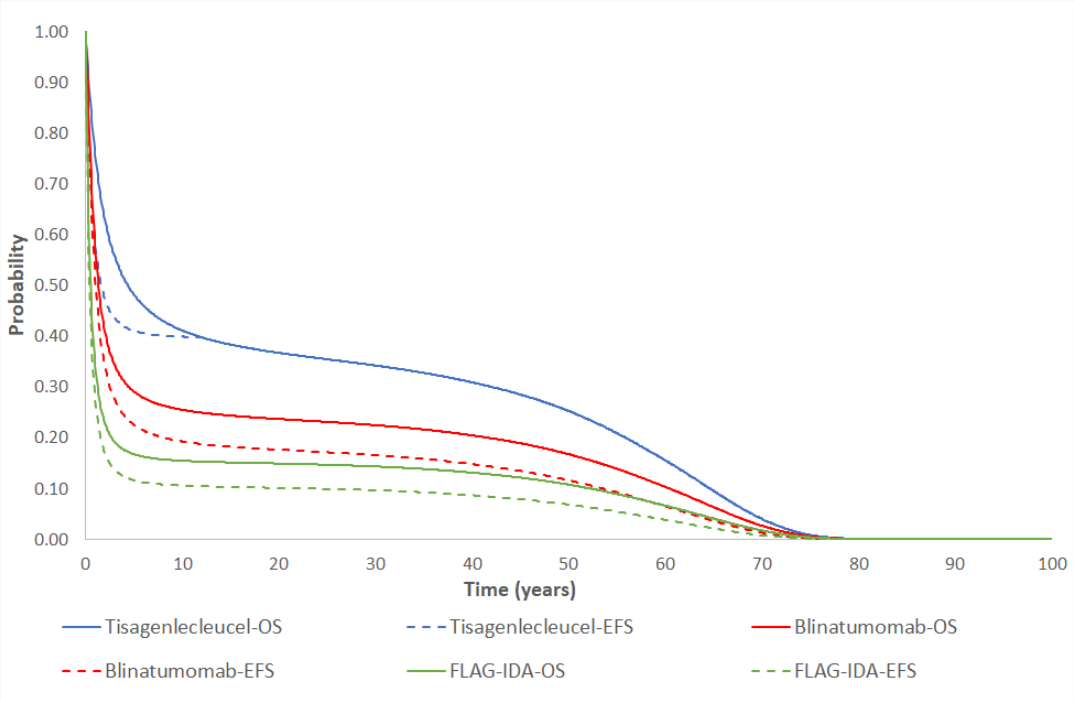


Survival models exclude general population mortality risks

The EAG also amended the allo-SCT rates for the blinatumomab and FLAG-IDA groups to reflect the SCT rates in RIALTO[47] and Kuhlen *et al.*[52] (53% for blinatumomab and 26% for FLAG-IDA).

The OS and EFS predictions from the EAG's preferred models are summarised in Figure 42.

Figure 42: EAG's preferred base case EFS and OS models, all treatment groups



OS - overall survival; EFS - event-free survival; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF
Modelled functions shown in the plot reflect the final model trace including general population mortality risks uplifted using an SMR of 4.0

EA4: Terminal care costs for patients dying prior to receiving the infusion

Within this analysis, terminal care costs of £13,198 were included for the 7.2% of patients who are assumed to die prior to receiving the tisagenlecleucel infusion.

EA5: IVIg treatment duration

The EAG amended the duration for which patients receive IVIg to reflect the AUC for EFS for tisagenlecleucel up to year 5, based on a suggestion from its clinical advisors. This AUC estimate was multiplied by 0.83, which reflects the proportion of tisagenlecleucel-treated patients in the pooled dataset who did not proceed to subsequent allo-SCT. This results in an assumed treatment duration of 25.5 months per patient receiving IVIg. The mean treatment duration per patient receiving the tisagenlecleucel infusion is therefore 7.7 months. This is similar to the expected treatment duration in the NHSE report (47% patients receiving IVIg for 18 months = 8.5 months).[37]

EA6: Updated unit costs from eMIT and BNF

Within this analysis, unit costs of lymphodepleting chemotherapy, bridging chemotherapy and FLAG-IDA were updated according to current values from eMIT and the BNF.

Table 53: Updated drug costs applied in EAG's preferred analysis

Drug	Original cost	Updated cost	Source
Lymphodepleting chemotherapy acquisition costs			
Fludarabine	£16.66	£15.88	eMIT 2023 (NPC Code: DHA371) fludarabine phosphate 50mg powder for solution for injection vials
Cyclophosphamide	£13.23	£12.96	eMIT 2023 (NPC Code: DHA014) cyclophosphamide 1g powder for solution for injection vials
Cytarabine	£8.28	£6.60	eMIT 2023 (NPC Code: DHA020) cytarabine 1g/10ml solution for injection vials
Etoposide	£3.94	£4.21	eMIT 2023 (NPC Code: DHA320) etoposide 100mg/5ml solution for injection vials
Bridging chemotherapy acquisition costs			
Allopurinol	£0.32	£0.31	eMIT 2023 (NPC Code: DJA084) allopurinol 100mg tablets
Dexamethasone	£2.46	£2.62	eMIT 2023 (NPC Code: DFN018) dexamethasone 2mg tablets
Vincristine	£8.34	£33.89	eMIT 2023 (NPC Code: DHA111) vincristine 2mg/2ml solution for injection vials
Intrathecal methotrexate	£2.35	£12.77	eMIT 2023 (NPC Code: DHA036) methotrexate 50mg/2ml solution for injection vials
Co-trimoxazole	£1.54	£0.98	eMIT 2023 (NPC Code: DEA224) co-trimoxazole 80mg/400mg tablets (480mg)
Salvage chemotherapy acquisition costs			
Fludarabine	£16.66	£15.88	eMIT 2023 (NPC Code: DHA371) fludarabine phosphate 50mg powder for solution for injection vials
Cytarabine	£8.28	£6.60	eMIT 2023 (NPC Code: DHA020) cytarabine 1g/10ml solution for injection vials
Idarubicin	£87.36	£41.47	BNF 2023, idarubicin hydrochloride 5mg
G-CSF	£56.84	£52.70	BNF 2023, filgrastim (accessed 14th Nov 2023)

eMIT - electronic Market Information Tool; BNF - British National Formulary; G-CSF - granulocyte colony-stimulating factor

EA7: EAG-preferred model (EA1-6 combined)

This analysis includes all individual exploratory analyses listed above. The EAG's preferred analysis was run using both the deterministic and probabilistic versions of the model. It should be noted that the Gompertz model selected for EFS in the tisagenlecleucel group does not appear to be entirely stable; this should be borne in mind when interpreting the results obtained from the probabilistic model.

Additional sensitivity analyses

The following additional sensitivity analyses were conducted using the deterministic version of the EAG's preferred model (EA7a).

- *ASA1a-d: Use of alternative evidence sources for blinatumomab and FLAG-IDA.* In ASA1a, outcomes for blinatumomab were based on a log-normal MCM fitted to data reported by von Stackelberg *et al.*[15] In ASA1b, outcomes for FLAG-IDA were based on a log-normal MCM fitted to data reported by Jeha *et al.*[14] In ASA1c, the less optimistic exponential MCM is applied to the RIALTO data.[47] In ASA1d, OS outcomes for FLAG-IDA are based on the average of Jeha *et al.* and Kuhlen *et al.* (note: the allo-SCT rate from Kuhlen *et al.* is retained in this scenario).
- *ASA2a-f: Alternative OS models.* The analysis was re-run using all alternative OS MCMs for the tisagenlecleucel group.
- *ASA3a-f: Alternative EFS models.* The analysis was re-run using all alternative EFS MCMs for the tisagenlecleucel group.
- *ASA4: Inclusion of MAIC-adjusted OS.* This analysis includes the MAIC-adjusted OS models for the tisagenlecleucel group. EFS is modelled using naïve comparisons as a MAIC was not conducted for this endpoint. The company's model does not include a MAIC-adjusted allo-SCT rate.
- *ASA5a-b: Alternative SMRs.* This analysis explores the use of alternative SMRs for the cured population. A lower SMR of 1.5 was suggested by one of the company's clinical experts. An upper SMR of 9.05 was applied, as per the company's model in TA554.[19]
- *ASA6: ELIANA utility values.* This analysis uses utility values from ELIANA.[34] This analysis applies the EF utility value to both alive states after 5 years.
- *ASA7: Lower allo-SCT disutility.* This analysis applies a disutility value of -0.02 for 12 months based on disutilities estimated from Sung *et al.*[74] for 3 months and from Felder-Puig *et al.*[90] for 9 months. This disutility is substantially lower than the value applied in the company's base case analysis.
- *ASA8: Reduced QALYs and costs for non-infused patients.* Within this analysis, the costs and QALYs attributed to patients who do not receive the tisagenlecleucel infusion are reduced by 90%.

- *ASA9: Lower allo-SCT costs.* Within this analysis, the costs of allo-SCT are arbitrarily reduced by 25%.
- *ASA10a-c: Duration of treatment for B-cell aplasia.* Within ASA10a, the model assumes that 47% of patients receive IVIg for a mean duration of 18 months, based on the NHSE SACT data. Within ASA10b, the duration of treatment for B-cell aplasia was doubled (from 25.5 months to 51 months). In analysis ASA10c, the full AUC for EFS was applied resulting in an IVIg treatment duration of 209.6 months. For ASA10b and ASA10c, the IVIg cost is applied to 30.4% of patients (40.5% patients get hypogammaglobulinaemia and 75% of these require IVIG).
- *ASA11: Costs of lymphodepleting chemotherapy removed.* Within this analysis the costs of lymphodepleting chemotherapy for non-infused patients were set equal to zero.
- *ASA12: Non-reference case discount rates.* In line with the analysis presented in the CS,[9] this scenario includes the use of lower discount rates for health outcomes and costs of 1.5%.

5.6 Results of the EAG's exploratory analyses

Results of the EAG's preferred analysis

The results of the EAG's preferred analyses are shown in Table 54. Each analysis is applied incrementally over the preceding analysis (i.e., EA3 also includes changes applied in EA1 and EA2). The EAG's exploratory analyses indicate that the correction of model errors has little impact on the model results (EA1). The use of the pooled tisagenlecleucel dataset reduces life years gained (LYGs), QALYs and costs for the tisagenlecleucel group, and increases the ICERs against both comparators (EA2). The inclusion of OS data for the comparator groups from RIALTO[47] and Kuhlen *et al.*[52] increases LYGs, QALYs and costs for both the blinatumomab and FLAG-IDA groups, and increases the ICERs for tisagenlecleucel against each comparator (EA3). The inclusion of a longer duration of IVIg treatment leads to fairly small increase in the ICER for tisagenlecleucel versus both comparators (EA5). The inclusion of terminal care costs for patients who die prior to receiving the tisagenlecleucel and updated unit drug acquisition costs have little impact on the model results (EA4 and EA6). Excluding QALY weighting, the EAG's preferred analysis leads to a probabilistic ICER for tisagenlecleucel versus blinatumomab of £45,052 per QALY gained and a probabilistic ICER for tisagenlecleucel versus FLAG-IDA of £43,947 per QALY gained. The deterministic ICERs are similar at £42,398 and £45,636 per QALY gained.

Based on the deterministic model, if tisagenlecleucel is evaluated within a fully incremental analysis, blinatumomab would be ruled out of the analysis due to extended dominance. This finding does not apply to the probabilistic version of the model.

Table 54: EAG's preferred model results, includes tisagenlecleucel PAS, excludes QALY weighting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER	DM
Company's original base case model (deterministic)								
Tisagenlecleucel	22.98	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	7.33	3.06	£158,289	15.65	[redacted]	[redacted]	**£19,218**	1.7
FLAG-IDA	5.55	2.22	£59,980	17.43	[redacted]	[redacted]	**£30,778**	1.7
EA1: Correction of model errors†								
Tisagenlecleucel	22.34	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	7.22	3.02	£158,278	15.12	[redacted]	[redacted]	**£18,909**	1.7
FLAG-IDA	5.54	2.21	£59,979	16.80	[redacted]	[redacted]	**£30,833**	1.7
EA2: Pooled tisagenlecleucel dataset, OS=log-logistic, EFS=Gompertz, plus pooled SCT rate and AE rates								
Tisagenlecleucel	18.64	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	7.22	3.02	£158,278	11.42	[redacted]	[redacted]	**£22,771**	1.7
FLAG-IDA	5.54	2.21	£59,979	13.10	[redacted]	[redacted]	**£36,970**	1.7
EA3: Alternative comparator studies and models: RIALTO blinatumomab, OS=log-logistic MCM, EFS=HR applied to OS model, allo-SCT rate=53% Kuhlen chemotherapy, OS=log-normal MCM, EFS=HR applied to OS model, allo-SCT rate=26%								
Tisagenlecleucel	19.25	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	14.44	5.91	£185,311	4.81	[redacted]	[redacted]	**£39,082**	1.2
FLAG-IDA	9.08	3.69	£77,497	10.17	[redacted]	[redacted]	**£43,910**	1.7
EA4: Inclusion of terminal care costs for patients dying prior to receiving the infusion								
Tisagenlecleucel	19.25	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	14.44	5.91	£185,311	4.81	[redacted]	[redacted]	**£39,518**	1.2
FLAG-IDA	9.08	3.69	£77,497	10.17	[redacted]	[redacted]	**£44,127**	1.7
EA5: IVIg treatment duration = 25.5 months								
Tisagenlecleucel	19.25	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	14.44	5.91	£185,311	4.81	[redacted]	[redacted]	**£42,368**	1.2
FLAG-IDA	9.08	3.69	£77,497	10.17	[redacted]	[redacted]	**£45,541**	1.7
EA6: Inclusion of updated unit costs from eMIT and BNF								
Tisagenlecleucel	19.25	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	14.44	5.91	£185,311	4.81	[redacted]	[redacted]	**£42,398**	1.2
FLAG-IDA	9.08	3.69	£77,143	10.17	[redacted]	[redacted]	**£45,636**	1.7
EA7a: EAG-preferred model (EA1-6 combined), deterministic								
Tisagenlecleucel	19.25	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	14.44	5.91	£185,311	4.81	[redacted]	[redacted]	**£42,398**	1.2
FLAG-IDA	9.08	3.69	£77,143	10.17	[redacted]	[redacted]	**£45,636**	1.7
EA7b: preferred model (EA1-6 combined), probabilistic								
Tisagenlecleucel	19.55	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab	15.37	6.27	£186,433	4.17	[redacted]	[redacted]	**£45,052**	1.2
FLAG-IDA	9.12	3.73	£77,098	10.43	[redacted]	[redacted]	**£43,947**	1.7

** Undiscounted*

† Includes errors corrected by the company in their revised model

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; DM - decision modifier; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; EFS - event-free survival; OS - overall survival; EA - exploratory analysis; MCM - mixture-cure model; allo-SCT - allogeneic stem cell transplantation; HR - hazard ratio; eMIT - electronic Market Information tool; BNF - British National Formulary; IVIg - intravenous immunoglobulin

Results of the EAG's additional sensitivity analysis

The results of the EAG's additional sensitivity analyses (ASAs) are shown in Table 55. These analyses suggest the following:

- The model results are sensitive to the source of OS data and allo-SCT rates for the comparator groups, particularly for the comparison against blinatumomab (ASAs 1a-d). The inclusion of either the OS data and the allo-SCT rate reported by von Stackelberg *et al.*,[15] or the use of a more pessimistic MCM fitted to the RIALTO OS data,[47] substantially reduces the ICER for tisagenlecleucel versus blinatumomab. The use of OS data and the SCT rate from Jeha *et al.*[14] also reduces the ICER for tisagenlecleucel versus FLAG-IDA, albeit to a lesser extent.
- The model results are sensitive to the use of alternative MCMs for OS in the tisagenlecleucel group (ASAs 2a-f). The ICERs are notably lower when the exponential MCM is used, and are substantially higher when the generalised gamma or log-normal MCMs are selected. The EAG's second clinical advisor preferred the exponential MCM.
- The inclusion of EQ-5D-3L data from ELIANA[34] increases the ICERs tisagenlecleucel versus each comparator by around £4,500 (ASA6).
- The inclusion of the NHSE data on IVIg use results has very little impact on the ICER (ASA10a). The inclusion of longer durations of IVIg has the propensity to increase the ICER considerably in extreme scenarios (ASA10c).
- The ICER for tisagenlecleucel versus blinatumomab is sensitive to the cost of allo-SCT; assuming a lower cost leads to a higher ICER for tisagenlecleucel (ASA9). This is because the allo-SCT rate is substantially higher for blinatumomab when data from RIALTO[47] are used in the model.
- The ICERs for tisagenlecleucel versus blinatumomab and FLAG-IDA are substantially lower when non-reference case discount rates of 1.5% are applied (ASA12).
- The model results are not particularly sensitive to the choice of EFS model, the SMR, the inclusion of the MAIC-adjusted OS for tisagenlecleucel, or the exclusion of the costs of lymphodepleting chemotherapy in non-infused patients.

Table 55: EAG's additional sensitivity analysis results, includes tisagenlecleucel PAS, excludes QALY weighting, deterministic

Scenario	Description	Tisagenlecleucel versus blinatumomab				Tisagenlecleucel versus FLAG-IDA			
		Inc. QALYs	Inc. Costs	ICER	DM	Inc. QALYs	Inc. Costs	ICER	DM
EA7a	**EAG preferred deterministic model**	[redacted]	[redacted]	**£42,398**	1.2	[redacted]	[redacted]	**£45,636**	1.7
ASA1a	Blinatumomab = von Stackelberg *et al.* (OS=log-normal MCM)	[redacted]	[redacted]	**£24,060**	1.7	[redacted]	[redacted]	**£47,039**	1.7
ASA1b	FLAG-IDA = Jeha *et al.* (OS=log-normal MCM)	[redacted]	[redacted]	**£43,618**	1.2	[redacted]	[redacted]	**£37,501**	1.7
ASA1c	Blinatumomab = RIALTO (OS=exponential MCM)	[redacted]	[redacted]	**£30,426**	1.7	[redacted]	[redacted]	**£46,176**	1.7
ASA1d	FLAG-IDA = average OS from Jeha and Kuhlen	[redacted]	[redacted]	**£43,265**	1.2	[redacted]	[redacted]	**£39,161**	1.7
ASA2a	Tisagen OS: MCM Exponential*	[redacted]	[redacted]	**£31,003**	1.2	[redacted]	[redacted]	**£38,579**	1.7
ASA2b	Tisagen OS: MCM Weibull	[redacted]	[redacted]	**£32,066**	1.2	[redacted]	[redacted]	**£39,332**	1.7
ASA2c	Tisagen OS: MCM Gompertz	[redacted]	[redacted]	**£35,559**	1.2	[redacted]	[redacted]	**£41,655**	1.7
ASA2d	Tisagen OS: MCM Log-normal	[redacted]	[redacted]	**£58,712**	1.2	[redacted]	[redacted]	**£52,929**	1.7
ASA2e	Tisagen OS: MCM Log-logistic	[redacted]	[redacted]	**£42,398**	1.2	[redacted]	[redacted]	**£45,636**	1.7
ASA2f	Tisagen OS: MCM Generalised gamma	[redacted]	[redacted]	**£66,931**	1.2	[redacted]	[redacted]	**£55,768**	1.7
ASA3a	Tisagen EFS: MCM Exponential	[redacted]	[redacted]	**£42,467**	1.2	[redacted]	[redacted]	**£45,672**	1.7
ASA3b	Tisagen EFS: MCM Weibull	[redacted]	[redacted]	**£42,409**	1.2	[redacted]	[redacted]	**£45,642**	1.7
ASA3c	Tisagen EFS: MCM Gompertz	[redacted]	[redacted]	**£42,398**	1.2	[redacted]	[redacted]	**£45,636**	1.7
ASA3d	Tisagen EFS: MCM Log-normal	[redacted]	[redacted]	**£42,271**	1.2	[redacted]	[redacted]	**£45,570**	1.7
ASA3e	Tisagen EFS : MCM Log-logistic	[redacted]	[redacted]	**£42,344**	1.2	[redacted]	[redacted]	**£45,608**	1.7
ASA3f	Tisagen EFS: MCM Generalised gamma	[redacted]	[redacted]	**£42,384**	1.2	[redacted]	[redacted]	**£45,629**	1.7
ASA4	Inclusion of MAIC-adjusted OS	[redacted]	[redacted]	**£42,398**	1.2	[redacted]	[redacted]	**£45,636**	1.7
ASA5a	Low excess mortality, SMR=1.5	[redacted]	[redacted]	**£40,845**	1.2	[redacted]	[redacted]	**£43,804**	1.7
ASA5b	High excess mortality, SMR=9.05	[redacted]	[redacted]	**£44,495**	1.7	[redacted]	[redacted]	**£48,122**	1.7
ASA6	ELIANA utility values	[redacted]	[redacted]	**£46,720**	1.7	[redacted]	[redacted]	**£50,644**	1.7
ASA7	Allo-SCT decrement from Felder-Puig *et al*	[redacted]	[redacted]	**£44,694**	1.2	[redacted]	[redacted]	**£45,897**	1.7
ASA8	Non-infused patients incur 10% of comparator QALYs, costs	[redacted]	[redacted]	**£46,758**	1.2	[redacted]	[redacted]	**£47,931**	1.7
ASA9	Allo-SCT cost reduced by 25%	[redacted]	[redacted]	**£48,283**	1.2	[redacted]	[redacted]	**£46,287**	1.7
ASA10a	IVIg given to 47% of patients for 18 months (mean AUC)	[redacted]	[redacted]	**£42,872**	1.2	[redacted]	[redacted]	**£45,872**	1.7
ASA10b	Duration of IVIg treatment doubled	[redacted]	[redacted]	**£47,552**	1.2	[redacted]	[redacted]	**£48,194**	1.7
ASA10c	Duration of IVIg treatment = mean EFS	[redacted]	[redacted]	**£79,612**	1.2	[redacted]	[redacted]	**£64,103**	1.7
ASA11	Costs of lymphodepleting chemo in non-infused patients = 0	[redacted]	[redacted]	**£42,000**	1.2	[redacted]	[redacted]	**£45,439**	1.7
ASA12	Discount rates = 1.5%	[redacted]	[redacted]	**£30,106**	1.2	[redacted]	[redacted]	**£32,134**	1.7

** This scenario reflects the EAG's second clinical advisor's preferred model*

ASA - additional sensitivity analysis; OS - overall survival; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; DM - decision modifier

Summary of ICERs including QALY weighting for disease severity

The results of the EAG's exploratory analyses including QALY weighting are summarised in Table 56. When QALY weighting is included, the probabilistic version of the EAG's preferred model suggests that the ICER for tisagenlecleucel versus blinatumomab is expected to be £37,543 per QALY gained, whereas the ICER for tisagenlecleucel versus FLAG-IDA is expected to be £25,851 per QALY gained. These ICERs are higher than the company's base case ICERs.

Table 56: Summary of EAG's exploratory analyses including QALY weighting

Scenario	Weighted ICER: Tisagenlecleucel vs blinatumomab	Weighted ICER: Tisagenlecleucel vs FLAG-IDA
Company's original base case, deterministic	**£11,304**	**£18,105**
Company's original base case, probabilistic	**£12,006**	**£17,665**
EAG's preferred deterministic analysis (EA7a)	**£35,332**	**£26,845**
EAG's preferred probabilistic analysis (EA7b)	**£37,543**	**£25,851**
ASA1a - Use of von Stackelberg *et al*. for blin (OS=log-normal)	£14,153	£27,670
ASA1b - Use of Jeha *et al*. for FLAG-IDA (OS=log-normal)	£36,349	£22,059
ASA1c - Blinatumomab = RIALTO (OS=exponential MCM)	£17,898	£27,162
ASA1d - FLAG-IDA = average OS from Jeha and Kuhlen	£36,054	£23,036
ASA2a - Tisagen OS: MCM Exponential	£25,836	£22,694
ASA2b - Tisagen OS: MCM Weibull	£26,721	£23,136
ASA2c - Tisagen OS: MCM Gompertz	£29,633	£24,503
ASA2d - Tisagen OS: MCM Log-normal	£48,927	£31,135
ASA2e - Tisagen OS: MCM Log-logistic	£35,332	£26,845
ASA2f - Tisagen OS: MCM Generalised gamma	£55,776	£32,805
ASA3a - Tisagen EFS: MCM Exponential	£35,390	£26,866
ASA3b - Tisagen EFS: MCM Weibull	£35,341	£26,848
ASA3c - Tisagen EFS: MCM Gompertz	£35,332	£26,845
ASA3d - Tisagen EFS: MCM Log-normal	£35,226	£26,806
ASA3e - Tisagen EFS: MCM Log-logistic	£35,286	£26,828
ASA3f - Tisagen EFS: MCM Generalised gamma	£35,320	£26,841
ASA4 - Inclusion of MAIC-adjusted OS	£35,332	£26,845
ASA5a - Low excess mortality, SMR=1.5	£34,037	£25,767
ASA5b - High excess mortality, SMR=9.05	£26,174	£28,307
ASA6 - ELIANA utility values	£27,482	£29,791
ASA7 - Allo-SCT decrement from Felder-Puig *et al.*	£37,245	£26,998
ASA8 - Non-infused patients incur 10% of comparator QALYs and costs	£38,965	£28,194
ASA9 - Allo-SCT cost reduced by 25%	£40,236	£27,228
ASA10a - 47% receive IVIg for 18 months	£35,727	£26,983
ASA10b - Duration of IVIg treatment doubled	£39,627	£28,349
ASA10c - Duration of IVIg treatment = mean EFS	£66,344	£37,708
ASA11 - Costs of lymphodepleting chemo in non-infused patients = 0	£35,000	£26,729
ASA12 - Discount rates = 1.5%	£25,088	£18,902

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio EA - exploratory analysis; ASA - additional sensitivity analysis

5.7 Discussion

The CS[9] presents an SLR of existing economic studies of paediatric and young adult patients aged under 25 years with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse, and the methods and results of the company's model-based health economic analysis of tisagenlecleucel within this indication.

The company's SLR identified six economic analyses of tisagenlecleucel for R/R B-cell ALL which were prioritised for inclusion in the review. The SLR also included two economic analyses of other treatments for R/R ALL. All of the identified economic analyses of tisagenlecleucel used a partitioned survival modelling approach; some of these studies also described the use of an initial decision tree component to account for costs and outcomes accrued by patients for whom the tisagenlecleucel infusion is planned but not received. All six studies were informed by a pooled dataset of tisagenlecleucel studies including ELIANA[34] and ENSIGN,[35] and in some cases B2101J.[36] Unexpectedly, the company's SLR did not include the model used to inform TA554.[19]

The company's submitted model assesses the cost-effectiveness of tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA for the treatment of paediatric and young adult patients with R/R B-cell ALL. This is consistent with the full marketing authorisation for tisagenlecleucel.[28] In keeping with several of the economic analyses included in the company's SLR, the company's model includes an initial decision tree component to account for outcomes and costs in patients who do not receive the tisagenlecleucel infusion. For those patients who receive the tisagenlecleucel infusion or the comparator treatments, the economic analysis uses a partitioned survival approach which includes three health states: (i) event-free; (ii) relapsed/progressed disease and (iii) dead. The analysis adopts an NHS and PSS perspective, including QALYs accrued by ALL patients; caregiver effects are not included. Clinical outcomes for the tisagenlecleucel group are based on MCMs fitted to data on EFS and OS from ELIANA.[34] Clinical outcomes for the blinatumomab and FLAG-IDA groups are based on OS data from single-arm studies (von Stackelberg *et al.*[15] and Jeha *et al.*[14]). EFS for blinatumomab and FLAG-IDA is estimated using an HR between OS and EFS estimated using data reported in the UK ALL study.[26] Health state utility values are based on data from a previous modelling study.[73] Resource costs are based on ELIANA, the NHSE CAR-T tariff, previous literature,[80] standard costing sources[37, 79] and clinical assumptions. Model results are presented in the form of pairwise comparisons between tisagenlecleucel and each comparator; a full incremental analysis is not presented.

The probabilistic version of the company's original model suggests that the ICER for tisagenlecleucel versus blinatumomab is £20,410 per QALY gained, whereas the ICER for tisagenlecleucel versus FLAG-IDA is £30,031 per QALY gained (excluding QALY weighting). The deterministic ICERs are

similar. Based on the characteristics of the model population (12 years of age, 43% female) and the estimated discounted QALYs for the blinatumomab and FLAG-IDA groups, the decision modifier is estimated to be 1.7 for both comparisons. Including QALY weighting in the calculations leads to a probabilistic ICER for tisagenlecleucel versus blinatumomab of £12,006 per QALY gained and a probabilistic ICER for tisagenlecleucel versus FLAG-IDA of £17,665 per QALY gained. Following the clarification process, the company submitted two revised versions of the economic model which include the correction of minor errors as well as additional functionality; the results of these updated models are similar to the company's original base case model.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG's main concerns regarding the company's economic model are summarised below:

- The company's model uses data only from ELIANA[34] (N=79) based on the company's justification that this study has longer follow-up than ENSIGN[35] and B2101J,[36] and that this was the pivotal study which informed the marketing authorisation for tisagenlecleucel.[28] The EAG does not consider this decision to be appropriate. Rather, the EAG believes that given the similarities in the design and populations across the three tisagenlecleucel studies, the full pooled dataset (N=200) should be used to inform the economic model. This would mean that all of the available data on tisagenlecleucel are used, including longer follow-up for all three tisagenlecleucel studies which has become available since TA554.[19]
- EFS outcomes for the tisagenlecleucel group of the company's model include censoring for allo-SCT and further anticancer therapy, and exclude other clinically relevant events (MRD-positivity and loss of B-cell aplasia). This EFS definition may exaggerate the absolute benefits of tisagenlecleucel. UK real-world data for patients treated with tisagenlecleucel suggest substantially lower EFS when a more stringent definition is used.[45] The impact of this issue on the ICER for tisagenlecleucel is unknown.
- The EAG believes that the company's selection of the studies to inform outcomes for the blinatumomab and FLAG-IDA groups (von Stackelberg *et al.*[15] and Jeha *et al*.[14]) is neither transparent nor well justified. Of particular note, the rates of subsequent allo-SCT rates in both of these studies are substantially lower than the rates expected by clinical experts consulted by the company and the EAG. Whilst none of the studies identified in the company's SLR perfectly align with the target population for tisagenlecleucel, the RIALTO study[16] may better reflect outcomes for patients receiving blinatumomab, whereas Kuhlen *et al.*[52] (or a scenario between Kuhlen *et al.* and Jeha *et al.*) may better reflect outcomes for patients receiving salvage chemotherapy.
- Given the absence of RCTs of tisagenlecleucel versus either blinatumomab or FLAG-IDA, ITCs are required. To this end, the company has undertaken unanchored MAICs for

tisagenlecleucel versus each comparator. However, the MAIC-adjusted tisagenlecleucel OS is very similar to the unadjusted tisagenlecleucel OS. The EAG does not believe that all relevant prognostic factors and treatment effect modifiers have been included and properly adjusted for. Including the MAIC-adjusted OS data in the economic model has virtually no impact on the model results.

- Given the limitations of the company's MAICs, the company's economic model is based on naïve ITCs between tisagenlecleucel and its comparators. These ITCs assume that there are no between-study differences in variables which influence outcomes. This assumption is unlikely to be appropriate.
- The EAG's clinical experts commented that it is likely that tisagenlecleucel is curative in some patients. The company's use of survival analyses in the economic model is restricted to MCMs only. These models force the distribution to include a cure fraction, which may result in unstable or unreliable parameter estimates if the duration of study follow-up or the number of observed events is insufficient. The EAG believes that it would have been useful to explore the use of alternative flexible models, such as RCS distributions, combined with a structural assumptions of a cure timepoint. This type of analysis has not been done.
- Additional data from SACT have resolved some uncertainty around the costs of IVIg replacement therapy for hypogammaglobulinaemia. The inclusion of longer durations of IVIg treatment results in less favourable ICERs for tisagenlecleucel.

The EAG also identified additional issues relating to model programming errors, as well as uncertainty around utility values, resource use and costs. These issues are comparatively less important.

The EAG undertook exploratory analyses using the company's second revised model to address some of the issues described above. The EAG's preferred model includes: (1) the correction of minor programming errors; (2) the use of MCMs fitted to data from pooled tisagenlecleucel dataset;[34-36] (3) the use of MCMs fitted to data from RIALTO[16] for blinatumomab and Kuhlen *et al.*[52] for FLAG-IDA, together with subsequent allo-SCT rates reported in these studies; (4) the inclusion of terminal care costs for patients who die prior to receiving the tisagenlecleucel infusion, and (5) a longer IVIg duration of 25.5 months. Excluding QALY weighting, the probabilistic version of the EAG's preferred model suggests that the ICER for tisagenlecleucel versus blinatumomab is expected to be £42,398 per QALY, whereas the ICER for tisagenlecleucel versus FLAG-IDA is expected to be £45,636 per QALY gained. Based on models fitted to OS data from RIALTO[16] and Kuhlen *et al.*,[52] the EAG's preferred analysis suggests decision modifiers of 1.2 for blinatumomab and 1.7 for FLAG-IDA. When QALY weighting is included in the model, the probabilistic ICER for tisagenlecleucel versus blinatumomab is expected to be £35,332 per QALY gained, whereas the probabilistic ICER for tisagenlecleucel versus FLAG-IDA is expected to be £26,845 per QALY gained. The deterministic ICERs are similar.

The EAG's additional sensitivity analyses indicate that the model results are sensitive to the choice of studies used to inform OS in the comparator groups, the choice of MCM for OS in the tisagenlecleucel and blinatumomab groups, the utility values applied to the EF and PD health states, the duration of IVIg treatment and the inclusion of non-reference case discount rates.

6 OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The CS[9] presents data on three single-arm studies of tisagenlecleucel (ELIANA,[34] ENSIGN[35] and B2101J[36]) in a total of 200 patients aged up to 25 years with B-cell ALL that is refractory, in relapse post-SCT, in second or later relapse, or ineligible for SCT. In addition, the NHSE SACT dataset[37] provides data on 121 patients receiving tisagenlecleucel in England during the managed access period. The proportion of patients receiving subsequent allo-SCT was 23% in ELIANA,[34] 14% in ENSIGN[35] and 14% in B2101J[36] (18% pooled across studies), and 11% in the NHSE dataset. Median EFS was 21 months across the three pooled clinical studies. Median OS was 48 months across the three pooled studies, while in the NHSE dataset, median OS was not reached (and 3-year OS was 67%). Frequent AEs included CRS (81%), hypogammaglobulinaemia (51%) and decreases in white blood cells (57%), neutrophils (52%) and platelets (47%).

The company conducted a MAIC for OS. The company preferred to include only the ELIANA[34] study for tisagenlecleucel, while the EAG considered that, given the similarities in design and populations, the pooled dataset including all three studies (N=200) should be used in the MAIC. The MAIC included two comparators: blinatumomab and salvage chemotherapy. For blinatumomab, the company used von Stackelberg *et al.,* 2016[15] (subsequent allo-SCT rate 34%; median OS 7.5 months). For salvage chemotherapy, the company used Jeha *et al.*, 2006[14] (subsequent allo-SCT rate 15%; median OS 3 months). The company's MAIC for tisagenlecleucel vs. blinatumomab gave an HR for OS of 0.32 (95% CI 0.21 to 0.48, $p<0.001$), while the MAIC for tisagenlecleucel vs. salvage chemotherapy gave an HR for OS of 0.20 (95% CI 0.14 to 0.31, $p<0.001$). The EAG has concerns that the company's selection of comparator studies was not transparent, that rates of subsequent allo-SCT in the selected comparator studies were lower than expected, and that not all relevant prognostic factors and treatment effect modifiers were included and properly adjusted for. The EAG's clinical advisors suggested that the RIALTO[47] study (subsequent allo-SCT rate 53%; median OS 14.6 months) may better reflect outcomes for patients receiving blinatumomab. For salvage chemotherapy, one of the EAG's clinical advisors suggested that the study by Kuhlen *et al*.[52] (subsequent allo-SCT rate 26%; median OS 6 months) may better reflect outcomes for FLAG-IDA, while another clinical advisor suggested that OS for FLAG-IDA may lie between the estimates reported by Jeha *et al.* and Kuhlen *et al*.

Cost-effectiveness conclusions

The company's model assesses the cost-effectiveness of tisagenlecleucel versus blinatumomab and tisagenlecleucel versus FLAG-IDA for the treatment of paediatric and young adult patients with R/R B-cell ALL. Results are presented as pairwise comparisons; a full incremental analysis is not preesnted. Excluding QALY weighting, the probabilistic version of the company's original model suggests that

the base case ICER for tisagenlecleucel versus blinatumomab is £20,410 per QALY gained. Based on a decision modifier of 1.7, the probabilistic ICER including QALY weighting is expected estimated to be £12,006 per QALY gained. Excluding QALY weighting, the probabilistic ICER for tisagenlecleucel versus FLAG-IDA is expected to be £30,031 per QALY gained. Based on a decision modifier of 1.7, the ICER including QALY weighting is estimated to be £17,665 per QALY gained.

The EAG's preferred analysis includes: (1) the correction of model errors; (ii) use of the pooled tisagenlecleucel dataset; (iii) OS and allo-SCT rates from RIALTO for blinatumomab and Kuhlen *et al.* for FLAG-IDA; (iv) the inclusion of terminal care costs for patients who die prior to receiving the tisagenlecleucel infusion; (v) a longer IVIg duration of 7.7 months per patient receiving the infusion (25.5 months x 30.4% patients) and (vi) updated drug acquisition costs. Excluding QALY weighting, the EAG's preferred probabilistic ICERs for tisagenlecleucel are estimated to be £45,052 per QALY gained for the comparison against blinatumomab, and £43,947 per QALY gained for the comparison against FLAG-IDA. Including QALY weighting, the ICERs are estimated to be £37,543 per QALY gained and £25,851 per QALY gained, respectively.

The EAG notes that there remains considerable uncertainty around the relative effectiveness of tisagenlecleucel versus its comparators due to the need to rely on naïve ITCs of single-arm studies. The EAG also notes uncertainty around the definition of EFS in the tisagenlecleucel studies which may exaggerate the absolute benefits of treatment. The impact of these factors on the cost-effectiveness of tisagenlecleucel is not known. Further data collection on the extent and duration of IVIg use in SACT has reduced some of the uncertainty around this aspect of the model.

7 REFERENCES

1. Leukemia Foundation. Acute lymphoblastic leukaemia. What is acute lymphoblastic leukaemia? Available from https://www.leukaemia.org.au/blood-cancer/leukaemia/acute-lymphoblastic-leukaemia/ [date accessed 17/11/2023]; 2023.
2. Cancer Research UK. What is acute leukoblastic leukaemia? Availabe from https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [date accessed 17/11/2023]; 2023.
3. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer Journal* 2017;30(7):e577.
4. Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet* 2020;395:1146-62.
5. Leukemia & Lymphoma Society. ALL subtypes. Available from https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/childhood-all/all-subtypes [date accessed 17/11/2023]; 2023.
6. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence statistics. Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all#heading-Zero [date accessed 17/11/2023]; 2023.
7. Cancer Research UK. Acute lymphblastic leukaemia (ALL) mortality statistics. Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/mortality#heading-One [date accessed 17/11/2023]; 2023.
8. Haematological Malignancy Research Network. Survival, B-cell ALL. Available from https://hmrn.org/statistics/survival [date accessed 17/11/2023]; 2023.
9. Novartis Pharmaceuticals Ltd. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]. Company's evidence submission; 2023.
10. Nguyen K, Devidas M, Cheng S-C, La M, Raetz EA, Carroll WL, *et al.* Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia* 2008;22(12):2142-50.
11. Pui C-H, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, *et al.* Childhood acute lymphoblastic leukemia: progress through collaboration. *Journal of Clinical Oncology* 2015;33(27):2938-48.
12. Ceppi F, Duval M, Leclerc J-M, Laverdiere C, Delva Y-L, Cellot S, *et al.* Improvement of the outcome of relapsed or refractory acute lymphoblastic leukemia in children using a risk-based treatment strategy. *PLoS One* 2016;11(9):e0160310.
13. Reismüller B, Peters C, Dworzak MN, Pötschger U, Urban C, Meister B, *et al.* Outcome of children and adolescents with a second or third relapse of acute lymphoblastic leukemia (ALL): a population-based analysis of the Austrian ALL-BFM (Berlin-Frankfurt-Münster) study group. *Journal of Pediatric Hematology/Oncology* 2013;35(5):e200-4.
14. Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, *et al.* Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2006;24(12):1917-23.
15. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, *et al.* Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2016;34(36):4381-9.
16. Locatelli F, Zugmaier G, Mergen N, Bader P, Jeha S, Schlegel PG, *et al.* Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. *Blood Advances* 2022;6(3):1004-14.
17. Essig S, von der Weid NX, Strippoli MP, Rebholz CE, Michel G, Rueegg CS, *et al.* Health-related quality of life in long-term survivors of relapsed childhood acute lymphoblastic leukemia. *PLoS One* 2012;7(5):e38015.

18. Sherief LM, Kamal NM, Abdalrahman HM, Youssef DM, Alhady MAA, Ali AS*, et al.* Psychological impact of chemotherapy for childhood acute lymphoblastic leukemia on patients and uheir parents. *Medicine (Baltimore)* 2015;94(51):e2280.
19. National institute for Health & Care Excellence. NICE Technology Appraisal Guidance 554: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. NICE: London; 2018.
20. National Institute for Health & Care Excellence. NICE Technology Appraisal Guidance 541: Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia. NICE: London.
21. National Institute for Health & Care Excellence. NICE Technology Appraisal Guidance 450: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. NICE: London.
22. National Institute for Health & Care Excellence. NICE Technology Appraisal Guidance 893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. NICE: London.
23. Children's Cancer Leukaemia Group. Clinical treatment guidelines. Available from: https://www.cclg.org.uk/what-we-do/clinical-treatment-guidelines [Date accessed: 12/11/2023].
24. Children's Cancer Leukaemia Group. UK Acute Lymphoblastic Leukaemia (UKALL) 2019 Interim Guidelines. Available from: https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/UKALL_2019_Interim_Guidance_Final.pdf [Date accessed09/11/2023]; 2019.
25. Pan-London Blood Cancer. Pan-London Haemato-Oncology Clinical Guidelines. Acute Leukaemias and Myeloid Neoplasms. Part 1: Acute Lymphoblastic Leukaemia. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-ALL-Guidelines-Jan-2020.pdf [Date accessed 06/11/2023]; 2020.
26. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV*, et al.* Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet* 2010;376(9757):2009-17.
27. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2023.
28. European Medicines A. Kymriah (tisagenlecleucel). Summary of Product Characteristics (SmPC). Available from: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf [Date accessed: 18/10/2023].
29. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]: Final scope. NICE: London; 2023.
30. Laetsch TW, Maude SL, Rives S, Hiramatsu H, Bittencourt H, Bader P*, et al.* Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. *Journal of Clinical Oncology* 2022;41(9):1664-9.
31. Novartis Pharmaceuticals Ltd. Date on File. Feedback from UK clinical experts. 2018.
32. National Institute for Health and Care Excellence. Reviewing our methods for health technology evaluation: consultation. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/chte-methods-consultation [Date accessed: 05/10/2023]. 2020
33. National Institute for Health and Care Excellence. NICE health technology evaluations: The manual. NICE: London; 2022.
34. Novartis Pharmaceuticals Ltd. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell

acute lymphoblastic leukemia. Clinical Study Report (17th November 2022 data cut-off). Data on File. 2023.

35. Novartis Pharmaceuticals Ltd. ENSIGN: A Phase II, single arm, multicenter study to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia. Clinical Study Report (24th May 2019 data cut-off). Data on File. 2019.
36. Novartis Pharmaceuticals Ltd. B2101J: A Phase I/IIA study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR zeta and 4-1BB signaling domains in subjects with chemotherapy resistant or refractory CD19+ leukemia and lymphoma. Clinical Study Report (7th May 2018 data cut-off). Data on File. 2019.
37. NHS England. Tisagenlecleucel for treating relapsed or refractory Philadelphia negative and positive B-cell acute lymphoblastic leukaemia in people aged 25 years and under – data review. London; 2023.
38. Novartis Pharmaceuticals Ltd. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]. Company's response to clarification questions from the EAG; 2023.
39. Novartis Pharmaceuticals Ltd. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID6290]. Company's evidence submission - appendices; 2023.
40. Dreyer NA, Bryant A, Velentgas P. The GRACE checklist: A validated assessment tool for high quality observational studies of comparative effectiveness. *Journal of Managed Care and Specialty Pharmacy* 2016;22(10):1107-13.
41. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M*, et al.* ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *British Medical Journal* 2016;355.
42. Centre for RaD. Systematic Reviews: CRD's guidance for undertaking reviews in health care. CRD: York: Centre for Reviews and Dissemination, University of York; 2008.
43. Maude SL, Pulsipher MA, Boyer MW, Grupp SA, Davies SM, Phillips CL*, et al.* Efficacy and safety of CTL019 in the first US Phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis. In: Blood (American Society of Hematology); 2016: 2801.
44. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ*, et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. *New England Journal of Medicine* 2014;371(16):1507-17.
45. Espuelas MO, Burridge S, Bonney D, Watts K, Roddie C, O'Reilly MA. Systematic intention to treat analysis of real-world outcomes in children and young adults receiving tisagenlecleucel: From elegibility through treatment failure. *Blood* 2022;140(Suppl1):2408-10.
46. Gore L, Locatelli F, Zugmaier G, Handgretinger R, O'Brien MM, Bader P*, et al.* Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. *Blood Cancer Journal* 2018;8(9):80.
47. Locatelli F, Zugmaier G, Mergen N, Bader P, Jeha S, Schlegel PG*, et al.* Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: Results of the RIALTO trial, an expanded access study. *Blood Cancer Journal* 2020;10(2):77.
48. Locatelli F, Zugmaier G, Rizzari C, Morris JD, Gruhn B, Klingebiel T*, et al.* Improved survival and MRD remission with blinatumomab vs. chemotherapy in children with first high-risk relapse B-ALL. *Leukemia* 2022;37(1):222-5.
49. Locatelli F, Maschan A, Boissel N, Strocchio L, Alam N, Pezzani I*, et al.* Pediatric patients with acute lymphoblastic leukemia treated with blinatumomab in a real-world setting: Results from the NEUF study. *Pediatric Blood Cancer* 2022;69(4):e29562.

50. Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, *et al.* Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. *Journal of the American Medical Association* 2021;325(9):833-42.
51. Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, *et al.* Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *New England Journal of Medicine* 2017;376(9):836-47.
52. Kuhlen M, Willasch AM, Dalle JH, Wachowiak J, Yaniv I, Ifversen M, *et al.* Outcome of relapse after allogeneic HSCT in children with ALL enrolled in the ALL-SCT 2003/2007 trial. *british Journal of Haematology* 2018;180(1):82-9.
53. Zwaan CM, Kowalczyk J, Schmitt C, Bielorai B, Russo MW, Woessner M, *et al.* Safety and efficacy of nelarabine in children and young adults with relapsed or refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of a Phase 4 study. *British Journal of Haematology* 2017;179(2):284-93.
54. Bertaina A, Vinti L, Strocchio L, Gaspari S, Caruso R, Algeri M, *et al.* The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukaemia of childhood. *British Journal of Haematology* 2017;176(4):629-36.
55. Miano M, Pistorio A, Putti MC, Dufour C, Messina C, Barisone E, *et al.* Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. *Leukemia & Lymphoma* 2012;53(9):1693-8.
56. Hijiya N, Thomson B, Isakoff MS, Silverman LB, Steinherz PG, Borowitz MJ, *et al.* Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Blood* 2011;118(23):6043-9.
57. Locatelli F, Testi AM, Bernardo ME, Rizzari C, Bertaina A, Merli P, *et al.* Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. *British Journal of Haematology* 2009;147(3):371-8.
58. Cooper TM, Razzouk BI, Gerbing R, Alonzo TA, Adlard K, Raetz E, *et al.* Phase I/II trial of clofarabine and cytarabine in children with relapsed/refractory acute lymphoblastic leukemia (AAML0523): a report from the Children's Oncology Group. *Pediatric Blood Cancer* 2013;60(7):1141-7.
59. Messinger YH, Gaynon PS, Sposto R, van der Giessen J, Eckroth E, Malvar J, *et al.* Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. *Blood* 2012;120(2):285-90.
60. Sun W, Malvar J, Sposto R, Verma A, Wilkes JJ, Dennis R, *et al.* Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia & lymphoma study. *Leukemia* 2018;32(11):2316-25.
61. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. DSU: Sheffield.
62. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 3rd edn: New York: Oxford University Press; 2015.
63. Haute Autorité de Santé. Blincyto (blinatumomab) Opinions on drugs - Economic opinion. Available from: https://has-sante.fr/jcms/p_3349491/en/blincyto-blinatumomab [Date accessed: 03/10/2023]. 2022. https://www.has-sante.fr/jcms/p_3312299/en/blincyto-blinatumomab#videotoc_1_1 (Accessed

64. Lis J, Kawalec P, Głasek M. Economic evaluation of acute lymphoblastic leukaemia treatment with clofarabine (Evoltra®) combined with chemotherapy for children and adolescents in Poland. *Journal of Health Policy and Outcomes Research* 2012:20-33.

65. Carey N, Leahy J, Trela-Larsen L, McCullagh L, Barry M. Tisagenlecleucel for relapsed/refractory acute lymphoblastic leukemia in the Irish healthcare setting: Cost-effectiveness and value of information analysis. *International Journal of Technology Assessment in Health Care* 2022;38(1).

66. Ribera Santasusana JM, de Andrés Saldaña A, García-Muñoz N, Gostkorzewicz J, Martínez Llinàs D, Díaz de Heredia C. Cost-effectiveness analysis of tisagenlecleucel in the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia in children and young adults in Spain. *ClinicoEconomics and Outcomes Research* 2020;12:253-64.

67. Moradi-Lakeh M, Yaghoubi M, Seitz P, Javanbakht M, Brock E. Cost-effectiveness of tisagenlecleucel in paediatric acute lymphoblastic leukaemia (pALL) and adult diffuse large B-cell lymphoma (DLBCL) in Switzerland. *Advances in Therapy* 2021;38(6):3427-43.

68. Thielen FW, van Dongen-Leunis A, Arons AM, Ladestein JR, Hoogerbrugge PM, Uyl-de Groot CA. Cost-effectiveness of anti-CD19 chimeric antigen receptor T-cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *European Journal of Haematology* 2020;105(2):203-15.

69. Scottish Medicines Consortium. Tisagenlecleucel (Kymriah). Available from: https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-fullsubmission-smc2129/. [Date accessed: 01/11/2023]. 2019. https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-fullsubmission-smc2129/ (Accessed

70. Norwegian Medicines A. Single technology assessent: Tisagenlecleucel (Kymriah) for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients. Available from: https://nyemetoder.no/Documents/Rapporter/Tisagenlecleucel%20(Kymriah)%20-%20hurtig%20metodevurdering.pdf [Date accessed: 06/10/2023]. 2018

71. Scottish Medicines Consortium. Blinatumomab 38.5 micrograms powder for concentrate and solution for solution for infusion (Blincyto®) Detailed advice. Available from: https://www.scottishmedicines.org.uk/media/4315/blinatumomab-blincyto-abbreviated-final-march-2019-for-website.pdf [date accessed 20/11/2023]. SMC; 2020. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.scottishmedicines.org.uk/media/5143/blinatumomab-blincyto-final-february-2020-for-website.pdf (Accessed 01/11/2023).

72. Office for National Statistics. Interim Life Tables: England & Wales Period expectation of life based on data for the years 2018-2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/interimlifetablesenglandandwales [Date accessed: 05/10/2023].

73. Kelly MJ, Pauker SG, Parsons SK. Using nonrandomized studies to inform complex clinical decisions: the thorny issue of cranial radiation therapy for T-cell acute lymphoblastic leukemia. *Pediatric Blood Cancer* 2015;62(5):790-7.

74. Sung L, Buckstein R, Doyle JJ, Crump M, Detsky AS. Treatment options for patients with acute myeloid leukemia with a matched sibling donor: A decision analysis. *Cancer* 2003;97(3):592-600.

75. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N*, et al.* The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technology Assessment* 2017;21(7):1-204.

76. Hernandez Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. DSU: Sheffield; 2022.

77. NHS England. NHS Reference Costs 2021-2022. National Schedule of NHS Costs 2021/22: The main schedule. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ [Date accessed: 14/10/2023].
78. Commercial Medicines Unit. Drugs and pharmaceutical electronic market information (eMIT). Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. [Date accessed: 01/12/2023].
79. Joint Formulary Committee. British National Formulary. Available from: https://bnf.nice.org.uk/ [Date accessed: 01/12/2023]. 2023
80. National Health Service Blood and Transplant. UK Stem Cell Strategy Oversight Committee. Unrelated donor stem cell transplantation in the UK: Effective affordable sustainable. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/29047/unrelated-donor-stem-cell-transplantation-in-the-uk-2014.pdf [Date accessed: 15/11/2023]. 2014
81. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology* 2012;12:9.
82. Nichol MB, Sengupta N, Globe DR. Evaluating quality-adjusted life years: estimation of the health utility index (HUI2) from the SF-36. *Medical Decision Marking* 2001;21(12):105-12.
83. National Cancer Comprehensive Network. Pediatric Acute Lymphoblastic Leukemia Guidelines. Available from: https://www.nccn.org/patients/guidelines/content/PDF/ped_all_patient.pdf [Date accessed: 13/11/2023]. 2023
84. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C*, et al.* Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR task force on good research practices—Modeling studies. *Value in Health* 2003;6(1):9-17.
85. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. DSU: Sheffield; 2013.
86. Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR. NICE DSU Technical Support Document 21 - Flexible methods for survival analysis. Sheffield; 2020.
87. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. *Pediatic Blood Cancer* 2007;48(4):460-7.
88. Aristides M, Barlev A, Barber B, Gijsen M, Quinn C. Population preference values for health states in relapsed or refractory B-precursor acute lymphoblastic leukemia in the United Kingdom. *Health Quality of Life Outcomes* 2015;13:181.
89. Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R*, et al.* Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *British Medical Journal* 2016;135(10):951-63.
90. Felder-Puig R, di Gallo A, Waldenmair M, Norden P, Winter A, Gadner H*, et al.* Health-related quality of life of pediatric patients receiving allogeneic stem cell or bone marrow transplantation: results of a longitudinal, multi-center study. *Bone Marrow Transplantation* 2006;38(2):119-26.
91. van Agthoven M, Groot MT, Verdonck LF, Löwenberg B, Schattenberg AV, Oudshoorn M*, et al.* Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. *Bone Marrow Transplantation* 2002;30(4):243-51.

8 APPENDICES

Appendix 1: Summary of AIC and BIC statistics and cure fractions for MCMs fitted to pooled tisagenlecleucel dataset, RIALTO and Kuhlen *et al.*

Table 57: AIC and BIC statistics and estimated cure fractions - pooled tisagenlecleucel dataset, RIALTO and Kuhlen *et al.*

	Tisagenlecleucel OS (Pooled dataset)			Tisagenlecleucel EFS (Pooled dataset)			Blinatumomab OS (RIALTO)			FLAG-IDA OS (Kuhlen *et al.*)		
	AIC	BIC	Cure fraction	AIC	BIC	Cure fraction	AIC	BIC	Cure fraction	AIC	BIC	Cure fraction
Exponential	920.07	926.66	44.3%	800.97	807.57	40.9%	181.79	187.19	20.4%	N/a	N/a	N/a
Weibull	921.96	931.85	43.5%	800.49	810.38	40.5%	181.63	189.73	40.6%	1380.73	1391.19	16.6%
Gompertz	921.14	931.03	27.8%	799.11	809.01	34.5%	N/a	N/a	N/a	N/a	N/a	N/a
Log-normal	918.81	928.71	26.7%	804.47	814.37	30.2%	N/a	N/a	N/a	1365.40	1375.87	15.2%
Log-logistic	920.05	929.95	34.0%	798.76	808.66	35.0%	181.57	189.68	23.4%	N/a	N/a	N/a
Generalised gamma	920.79	933.99	22.1%	801.57	814.77	39.8%	N/a	N/a	N/a	1366.67	1380.63	14.9%

OS - overall survival; EFS - event-free survival; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/a - not applicable

Single Technology Appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 18 December 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Section 1: Factual inaccuracies

Issue 1 Clarification of modelling of comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Section 1: "For tisagenlecleucel, EFS and OS are modelled using MCMs fitted to data from ELIANA. For blinatumomab and FLAG-IDA, OS is modelled using data from von Stackelberg *et al.* and Jeha *et al.*, respectively."	Please amend as follows: "For tisagenlecleucel, EFS and OS are modelled using MCMs fitted to data from ELIANA. For blinatumomab and FLAG-IDA, OS is modelled using **MCMs fitted to** data from von Stackelberg *et al.* and Jeha *et al*., respectively."	MCMs were fitted to the intervention and both comparators (in the case of OS), which is not made clear in this instance. Clarification here would ensure a balanced perspective on the choice of survival models is given.	The EAG agrees. The text has been amended the text for clarity.

Issue 2 Use of ELIANA EQ-5D data in the company analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Section 1: "Health state utility values are based on external literature (Kelly *et al.*), rather than the Euroqol 5-Dimensions (EQ-5D) data collected in ELIANA."	Please amend as follows: "**In the base case analysis,** health state utility values are based on external literature (Kelly *et al.*), rather than the Euroqol 5-Dimensions (EQ-5D) data collected in ELIANA."	The executive summary omits mention of the scenario analysis presented in the company submission (CS), in which ELIANA utility values are used to inform quality of life (QoL) in the model. Whilst this is noted further in the EAG report, it is important to include this scenario analysis	This is not a factual inaccuracy. The EAG does not believe this amendment is necessary. Uncertainty around the health state utility values used in the model is already discussed under Issue 4 on page 20. The report has not been amended.

		when discussing QoL data in the executive summary.	

Issue 3 Omission of company's justification for using ELIANA efficacy data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 1 Table, Section 1, Page 18: The EAG's key issue omits the reasoning provided by the company regarding the use of ELIANA trial data only in the economic model.	The company's reasons for using ELIANA rather than pooled trial data should be included, in particular further discussion of the company's response to EAG's clarification question (CQ) C1. Please consider amending along the following lines: "However, the company's economic model is informed by data from ELIANA only, based on the latest DCO (November 2022), **on the basis that the ERG in TA554 highlighted key differences between trials and data as an issue. The company therefore attempted to resolve this issue by using longer follow-up data from ELIANA**. Whilst patients enrolled in ENSIGN and B2101J **were similar in some characteristics** to those in ELIANA, these data are not used in the economic model. This substantially reduces the sample size and excludes relevant data (ELIANA only N=79; pooled dataset N=200)."	The EAG report does not transparently reflect one of the main drivers for the company's decision to use ELIANA only, which was the company's approach in response to criticism by the ERG from TA554. Section B.2.3.3 of the CS notes that, as noted by the Evidence Review Group (ERG) in the original submission for tisagenlecleucel in the treatment of r/r B-cell ALL (TA554), there are differences in Karnofsky/Lanksy performance status and number of patients who had not received a previous SCT.[1] Patients in the B2101J trial had higher Karnofsky/Lanksy performance status with 66.7% having a score of 100 compared to patients in the ELIANA and ENSIGN trials (38.0% and 28.1% respectively). Karnofsky/Lanksy performance status was identified by the ERG as a significant prognostic	This is not a factual inaccuracy. The EAG does not believe that the company's decision for using ELIANA only has been clearly justified – in particular: • The ERG report for TA554 highlighted uncertainty around survival and/or the need for longer follow-up for all three tisagenlecleucel studies. Longer follow-up data are available for all three tisagenlecleucel studies since TA554. The EAG believes that pooling the data here would have helped to address the TA554 ERG's concerns – including all three studies in a pooled dataset means that all relevant data are used in the model based on the maximum follow-up duration in each individual study. • The ERG report for TA554 does

Page 87, Section 4.10: "The EAG prefers the use of pooled tisagenlecleucel data over the use of ELIANA study alone as the pooled dataset has a larger sample size than the ELIANA study and the baseline characteristics of the pooled dataset are considered generally representative of the population of patients treated with tisagenlecleucel in the NHS."	Please consider adding mention of key differences across the pooled studies, such as Karnofsky/Lanksy performance status and number of patients who had not received a previous SCT. Furthermore, notwithstanding the view formed by the current EAG, it would be helpful to clarify that these were issues raised by the ERG in TA554 and that the company's decision to use ELIANA alone was partly as a response to the critique in TA554.	factor, thereby limiting the comparability of B2101J with ELIANA and ENSIGN.[1] With the exception of page 137 of the EAG report, no mention of the company's reasoning is made throughout the report. These updates should be incorporated to ensure an accurate reflection of the rationale behind the choice of efficacy data is provided in the report.	not suggest that the differences between the tisagenlecleucel studies represent a key issue. On the contrary, it states *"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 company's suggested amendment has not been made in the final EAG report.

Issue 4 Definition of EFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 2 Table, Section 1, Page 19: "As a consequence of this issue, the model results presented by the company and the EAG may be considered to be optimistic."	This sentence should be omitted, or relevant caveats around this prediction added for transparency. Throughout the EAG report, conclusions around the impact of the ELIANA EFS definition on cost-effectiveness results should be reconsidered accordingly.	Whilst the company acknowledge that use of a stricter definition of EFS would likely reduce the EFS probabilities for tisagenlecleucel in the economic model, the EAG have not provided any evidence that the use of this EFS definition would result in optimistic cost-effectiveness results. There are multiple reasons why this may not be the case, as outlined below, so any	The EAG notes that this issue relates both to the events which are counted as part of the endpoint (e.g., relapse, death, MRD-positivity) and which events are censored (e.g., no event at last follow-up, receipt of allo-SCT, receipt of further anticancer therapy). The former will affect how many events are counted, whereas the latter will remove

Section 4.2.2, Page 43, paragraph 2.	The discussion of EFS definition and any resulting bias in favour of tisagenlecleucel should include discussion of comparator EFS definition.	predictions relating the impact on cost-effectiveness results should either be omitted, or at minimum include the necessary caveats: • The source that informs comparator EFS evidence in the economic model (Parker *et al.* [2010]) appears to use an EFS definition similar to ELIANA, i.e. MRD-positivity, subsequent SCT or further therapy are not reported to be events for progression-free survival (which was used to inform the HR between OS and EFS in the economic model).[2] Progression-free survival was defined as time from randomisation to the first of induction failure (5% blasts or more in bone marrow at first timepoint, persistence of CSF blasts, non-regression of testicular enlargement), relapse, death from any cause, or a second malignancy.[2] AS such, EFS benefit for comparators in the model may also be exaggerated. The impact of using a more stringent EFS definition across tisagenlecleucel and comparators on relative effect remains highly uncertain, and the potential impact on cost-	patients from being at risk at the point of censoring. Both of these factors will affect EFS. The stricter definition of EFS in Espuelas *et al.* counts a more comprehensive range of clinical events and excludes censoring for further therapy. Parker *et al.* does not include MRD-positivity as an event, but it also does not appear to censor patients for allo-SCT or other further therapy, except in specific analyses. This appears to differ from how EFS was defined in ELIANA. Given that EFS outcomes for blinatumomab and FLAG-IDA are already based on an HR drawn from Parker, which are then applied to the OS from clinical studies of these treatments to derive EFS, and then compared naively against ELIANA, it goes without saying that these EFS estimates are already highly uncertain. The EAG agrees that using a more stringent definition of EFS would also have implications for the applicability of the utility values from both Kelly and ELIANA and that the direction and magnitude of the effect is unclear. In the Executive Summary and throughout the EAG report, the text already states that the impact of this issue on the ICER is unclear. The EAG
Page 88, Section 4.11: "This approach may exaggerate the benefits of tisagenlecleucel if subsequent allo-SCT was due to MRD-positivity or loss of B-cell aplasia, as this may indicate that the treatment has failed but this failure would be masked by the censoring mechanism."	Please consider amending as follows: "This approach may exaggerate the **absolute** benefits of tisagenlecleucel if subsequent allo-SCT was due to MRD-positivity or loss of B-cell aplasia, as this may indicate that the treatment has failed but this failure would be masked by the censoring mechanism. **The impact on relative treatment effect on the cost-effectiveness of tisagenlecleucel are unclear.**"		
Page 138, Section 5.3.5: "These plots also do not remove the effect of censoring for further therapy. Had a more stringent EFS definition been used, the EAG expects that this would lower the modelled tisagenlecleucel EFS function, which in turn, would reduce the mean utility	As with the examples above, the sentence should be amended to reflect: • The impact of tisagenlecleucel treatment effect relative to the modelled comparators is unknown • A more stringent definition of EFS would		

gains in the first 5 years and increase the proportion of patients incurring the higher PD state follow-up costs for the tisagenlecleucel group."	lead to reduced treatment IVIg treatment costs in the EAG's analysis • The overall impact on incremental QALYs and costs is unclear	effectiveness results is therefore unclear. • The source of evidence for the utility values informing the base case (Kelly *et al.* [2015]) appears to use an EFS definition similar to ELIANA, i.e. MRD-positivity, subsequent SCT or further therapy are not reported to be EFS events.[3] Utility data derived from the ELIANA trial reflect the EFS definition that excludes these events. It is therefore unlikely that either set of utility values in the model would be appropriate to inform health states based on a stricter definition of EFS. Any amendment to ELIANA EFS would therefore lead to a discrepancy in definition of EFS across efficacy and utility in the model. Additionally, adjustment to the current utility values included in the model reflecting a stricter definition of EFS (e.g. higher PD values to reflect observations previously categorised as EFS) may have an impact on ICERs opposite to the lowering of tisagenlecleucel EFS. As such, the EAG's statement that the definition of EFS may exaggerate the benefits of tisagenlecleucel are unfounded. • Regardless, the choice of parametric extrapolation for EFS for	has amended the text slightly to state that *"the model results presented by the company and the EAG might be optimistic."* In addition, we have clarified that the ELIANA definition will exaggerate absolute EFS benefits in the tisagenlecleucel group.
Page 169, Section 6: "The EAG also notes uncertainty around the definition of EFS in the tisagenlecleucel studies which may exaggerate the benefits of treatment."	Please consider amending as follows: "The EAG also notes uncertainty around the definition of EFS in the tisagenlecleucel studies which may exaggerate the **absolute** benefits of treatment. **However, impact of the definition of EFS on the relative benefits of tisagenlecleucel are unclear.**"		

		tisagenlecleucel and comparators was based on UK clinician estimates of long-term EFS, thus should accurately reflect expected EFS in UK clinical practice. • Additionally, in the EAG's preferred analysis, IVIg duration is based on a 5-year restricted mean AUC estimate of EFS from the pooled tisagenlecleucel trials. Applying a stricter definition of EFS would result in a reduced estimate IVIg treatment duration under this approach, thereby reducing costs associated with tisagenlecleucel and improving cost-effectiveness results.	

Issue 5 Comparator outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 3 Table, Section 1, Page 19: "The company has selected studies to represent outcomes for blinatumomab and FLAG-IDA in which allo-SCT rates were lower and OS outcomes	Please consider amending as follows: "The company has selected studies to represent outcomes for blinatumomab and FLAG-IDA in which allo-SCT rates were lower and OS outcomes were poorer than would be expected in patients who would otherwise be eligible for tisagenlecleucel in clinical	The CS notes at length (Section B.3.2.3) that the current submission deals with a hypothetical situation in which tisagenlecleucel is not available in clinical practice. Clinical expert feedback has confirmed that since its introduction via the	This is not a factual inaccuracy. The argument referred to in this table is made in the CS. When we asked our clinical advisors about expected survival outcomes for patients receiving blinatumomab or salvage chemotherapy, we asked about patients who would

were poorer than would be expected in patients who would otherwise be eligible for tisagenlecleucel in clinical practice."	practice. **The company has noted that, following the introduction of tisagenlecleucel, patients receiving blinatumomab or FLAG-IDA in current clinical practice are likely to have achieved higher rates of allo-SCT and experience better survival than in a world without tisagenlecleucel.**"	Cancer Drugs Fund (CDF), tisagenlecleucel has changed the way in which blinatumomab and salvage chemotherapy are used. Patients who are not good candidates for allo-SCT, such as those who have relapsed following prior allo-SCT (estimated to be approximately 50% of patients considered for tisagenlecleucel) or those who are chemo-refractory, are likely to be strong candidates for treatment with tisagenlecleucel. In contrast, comparator treatments such as blinatumomab are primarily used with the aim of achieving CR to successfully bridge to subsequent allo-SCT (resulting in higher rates of allo-SCT and improved OS). This justification is omitted throughout the EAG report.	otherwise be eligible for tisagenlecleucel. The EAG is unsure exactly what questions the company asked the clinical experts that they sought input from.
Section 4.8.3, Page 65: "The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after blinatumomab in clinical practice as 56.7%. The EAG's clinical advisors considered that the subsequent SCT rate, and therefore the median OS, in RIALTO[47] are more representative of clinical practice than those in von Stackelberg et al.[15] and NEUF[49]."	Please consider amending as follows: "The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after blinatumomab in clinical practice as 56.7%. The EAG's clinical advisors considered that the subsequent SCT rate, and therefore the median OS, in RIALTO[47] are more representative of clinical practice than those in von Stackelberg et al.[15] and NEUF[49]." **The CS notes that clinical expectations of allo-SCT rates following treatment with blinatumomab may be overestimated following the introduction of tisagenlecleucel as the preferred treatment option in UK ALL clinical practice.**"		This is not a factual inaccuracy. This sentence refers to the advice received from the EAG's clinical advisors, rather than the arguments made in the CS. The EAG report has not been amended.
Section 4.8.4, Page 65: "The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after	Please consider amending as follows: "The company's clinical validation report,[27] using estimates from three clinical experts, estimates the subsequent allo-SCT rate after salvage chemotherapy in clinical practice as 38.3%. **The CS notes that clinical**		This is not a factual inaccuracy. The cited text refers to the estimates provided in the company's clinical validation report. The clinical validation report does not provide any suggestion

salvage chemotherapy in clinical practice as 38.3%."	**expectations of allo-SCT rates following treatment with salvage chemotherapy may be overestimated following the introduction of tisagenlecleucel as the preferred treatment option in UK ALL clinical practice**"		that allo-SCT rates following salvage chemotherapy provided by the company's clinical experts are overestimates. The EAG has not been amended.
Page 139, Section 5.3.5: "The EAG's clinical advisors commented that the proportion of patients receiving allo-SCT and the resulting survival curves reported in von Stackelberg *et al.*[15] and Jeha *et al.*[14] are lower than would be expected in NHS practice for patients receiving blinatumomab and FLAG-IDA."	As with the examples above, please consider adding additional context, reflecting the fact that current clinical expectations of subsequent rates of allo-SCT for the comparators are likely to be overestimated compared to a world without tisagenlecleucel, which is the hypothetical situation of interest in this submission.		This is not a factual inaccuracy. Please refer to the previous EAG responses in this table.
Page 149, Section 5.3.5: "The rate of allo-SCT following blinatumomab is assumed to be 34.3% which is substantially higher than the rate suggested by NHSE in TA554, but lower than the rates suggested by clinical advisors to the company and the EAG (50% or higher)."	As with the examples above, please consider adding additional context, reflecting the fact that current clinical expectations of subsequent rates of allo-SCT for the comparators are likely to be overestimated compared to a world without tisagenlecleucel, which is the hypothetical situation of interest in this submission. In this instance, the rates of allo-SCT suggested by NHSE in TA554 (i.e. prior to the introduction of tisagenlecleucel), are likely to be more relevant to this submission.		This is not a factual inaccuracy. Please refer to the previous EAG responses in this table.

Page 165, Section 5.7: "Of particular note, the rates of subsequent allo-SCT rates in both of these studies are substantially lower than the rates expected by clinical experts consulted by the company and the EAG."	As with the examples above, please consider adding additional context, reflecting the fact that current clinical expectations of subsequent rates of allo-SCT for the comparators are likely to be overestimated compared to a world without tisagenlecleucel, which is the hypothetical situation of interest in this submission.		This is not a factual inaccuracy. Please refer to the previous EAG responses in this table.
Page 168, Section 6: The EAG has concerns that the company's selection of comparator studies was not transparent; that rates of subsequent allo-SCT in the selected comparator studies were lower than expected; […]"	As with the examples above, please consider adding additional context, reflecting the fact that current clinical expectations of subsequent rates of allo-SCT for the comparators are likely to be overestimated compared to a world without tisagenlecleucel, which is the hypothetical situation of interest in this submission.		This is not a factual inaccuracy. Please refer to the previous EAG responses in this table.

Issue 6 Source of IVIg treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 5 Table, Section 1: "These patients are assumed to require treatment for 11.4 months, based on the median time to B-cell recovery in the 2017 data-cut of ELIANA. The more recent 2022 data-cut of ELIANA suggests that median	Please amend as follows: "These patients are assumed to require treatment for 11.4 months, based on the median time to B-cell recovery in the 2017 data-cut of ELIANA. The more recent 2022 data-cut of ELIANA suggests that median time to B-cell recovery was 38.6 months, which is substantially longer than the	The EAG report's executive summary of Issue 5 omits the company's reasoning for not using the latest median time to B-cell recovery. This should be reported for transparency.	This is not a factual inaccuracy. However, the suggested text has been added to the EAG report to aid clarity.

time to B-cell recovery was 38.6 months, which is substantially longer than the company's estimate."	company's estimate. **Clinical expert feedback to the company however noted that 38.6 months was a much longer duration of treatment than would be expected in clinical practice.**"		

Issue 7 Discrepancy in mean IVIg treatment duration reported in NHSE report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 5 Table, Section 1, Page 21: "Based on the SACT data, 47% of patients receive IVIg for a mean duration of 18 months, […]"	Please amend as follows: "Based on the SACT data, 47% of patients receive IVIg for a mean duration of **13.3 months (amended to 18 months by EAG additional AUC calculations)**[…]"	There is a discrepancy between the mean IVIg treatment duration in the SACT report (13.3 months) and the IVIg treatment duration the EAG has calculated from the SACT report based on the AUC (18 months). Given that both the EAG report and the SACT report will be published on the NICE website, it is important to clarify the source of the discrepancy: that the EAG's stated mean duration of 18 months is based on additional calculations, which haven't been validated by SACT analysts. .	This is not a factual inaccuracy. The EAG believes that the NHSE estimate of mean IVIg use has been calculated as a crude mean of event times and censoring times. This is incorrect as it fails to properly account for the impact of censoring. For time-to-event data, the mean estimate should be calculated as the area under the curve. This issue has been clarified once in the Executive Summary (Issue 5) and once in Section 5.3.5 of the EAG report.
Table 3, Section 1, Page 24: "ASA10a - IVIg given to 47% of patients for 18 months"	Please amend as follows: "ASA10a - IVIg given to 47% of patients for **13.3 months (amended to 18 months by EAG additional AUC calculations)**"		
Page 151, Section 5.3.5: "Amongst 121 patients who received the tisagenlecleucel infusion, 57 patients (47.1%) received IVIg treatment. The area under the Kaplan-Meier	Please amend as follows: "Amongst 121 patients who received the tisagenlecleucel infusion, 57 patients (47.1%) received IVIg treatment**, with a mean treatment duration of 13.3 months**		

curve for time to treatment discontinuation for these 57 patients suggests a mean IVIg duration of approximately 18 months."	**(amended to 18 months by EAG additional AUC calculations)**"		
Page 157, Section 5.5: "This is similar to the expected treatment duration in the NHSE report (47% patients receiving IVIg for 18 months = 8.5 months).[37]"	Please amend as follows: "This is similar to the expected treatment duration in the NHSE report (47% patients receiving IVIg for **13.3 (ammended to 18 months by EAG additional AUC calculations** months = **8.5** months).[37]"		
Page 159, Section 5.5: "This is similar to the expected treatment duration in the NHSE report (47% patients receiving IVIg for 18 months = 8.5 months).[37]"	Please consider amending the text and the scenario described as follows: "Within ASA10a, the model assumes that 47% of patients receive IVIg for a mean duration of **13.3 months (ammended to 18 months by EAG additional AUC calculations)**, based on the NHSE SACT data."		

Issue 8 Patients reporting EQ-5D data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4, Page 37: "HRQoL data from one of the tisagenlecleucel studies (ELIANA) are reported in the	Please amend as follows: "HRQoL data from one of the tisagenlecleucel studies (ELIANA) are reported in the clinical and economic	The EAG reports that EQ-5D was assessed on in "subgroups" of patients in the ELIANA trial. It is more accurate to state that EQ-5D data were collected in patients	The EAG agrees and notes that the same issue applies to data collected using PedsQL data as

clinical and economic sections of the CS, albeit for subgroups of the population.”	sections of the CS, albeit **for patients 8 years of age or more**.”	8 and above, given no questionnaires are adapted for younger patients.	well the EQ-5D. The text has been amended.

Issue 9 “Traditional” definitions of EFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2, Page 44: “The EAG’s clinical advisors raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from traditional definitions of EFS.”	Please amend as follows: “The EAG’s clinical advisors raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from **other** definitions of EFS **used**.”	In the UK study cited by the EAG, the ELIANA definition is described as the "classic" definition, whereas including additional MRD-based events is described as a more stringent definition. It is therefore misleading to suggest that the definition of EFS used in ELIANA deviates from commonly used definitions of EFS.	The EAG agrees with wording this more neutrally. The text has been amended as follows: *“Clinical advisors to the EAG raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from **more stringent** definitions of EFS."*
Page 88, Section 4.11: “Clinical advisors to the EAG raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from traditional definitions of EFS.”	Please amend as follows: “Clinical advisors to the EAG raised concerns that the definition of EFS used in the tisagenlecleucel studies differs from **other** definitions of EFS **used**.”		The text has been amended as above.

Issue 10 Comparison of ELIANA EFS with and without censoring

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.2, Page 51: "The median EFS (with censoring for allo-SCT) in ELIANA, ENSIGN and B2101J was 24 months, 16 months and 25 months, with a pooled EFS of 21 months."	Please amend as follows: "The median EFS (with censoring for allo-SCT) in ELIANA, ENSIGN and B2101J was 24 months, 16 months and 25 months, with a pooled EFS of 21 months. **Results for EFS without censoring for allo-SCT were similar.**"	The EAG report presents Kaplan-Meier plots for EFS without censoring for allo-SCT in Figure 7 of its report, which indicate similar EFS with censoring for allo-SCT. Addition of this comparison should be included for transparency.	The EAG considers that if a comment is made regarding EFS results without censoring for allo-SCT, then a comment should also be made regarding censoring for further therapy. The text has been amended as follows: *"The median EFS (with censoring for allo-SCT) in ELIANA, ENSIGN and B2101J was 24 months, 16 months and 25 months, with a pooled EFS of 21 months.* ***Results for EFS without censoring for allo-SCT appeared similar. However, results for EFS without censoring for further therapy were not available.****"*

Issue 11 Comparison of baseline blast counts

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.8.3, Page 64: "As noted in the Evidence Review Group (ERG) report in TA554, the ELIANA and ENSIGN studies required patients to have ≥5% bone marrow blasts, whereas von Stackelberg et al. specified >25% bone marrow blasts."	Please amend as follows: "As noted in the Evidence Review Group (ERG) report in TA554, the ELIANA and ENSIGN studies required patients to have ≥5% bone marrow blasts, whereas von Stackelberg et al. specified >25% bone marrow blasts. **However, as shown in Table 24 of the CS, baseline blast counts were similar across the ELIANA and von Stackelberg et al. studies."**	The EAG report omits comparison of the baseline blast counts when discussing the differences between study eligibility criteria. These are only of concern if they lead to materially different patient characteristics.	The EAG agrees, but also considers that a little more detail of the comparison should be added. The text has been amended as follows: *"As noted in the Evidence Review Group (ERG) report in TA554, the ELIANA and ENSIGN studies required patients to have ≥5% bone marrow blasts, whereas von Stackelberg et al. specified >25% bone marrow blasts.* ***However, as shown in Table 24 of the CS, the proportions of patients with baseline blast counts >50% were similar across the ELIANA and von Stackelberg et al. studies (68% and 74% of patients, respectively)."***

Issue 12 Proportion of patients with ≥3 remissions/relapses in tisagenlecleucel studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.8.3, Page 64: "However, the EAG notes that the proportion with ≥3 remissions/relapses was 34% in the pooled tisagenlecleucel studies and 11% in von Stackelberg et al., which would indicate a fitter population in the tisagenlecleucel studies, while the proportion with refractory disease is not reported in the CS for the tisagenlecleucel studies."	Please omit this sentence.	There is considerable evidence that outcomes for patients worsen after each subsequent relapse. Therefore, the higher proportion of patients with ≥3 remissions/relapses in the pooled tisagenlecleucel studies would indicate a *less fit* population than in the von Stackelberg *et* al. study. The EAG's statement here is therefore factually inaccurate, and should therefore be removed.	The EAG agrees; this is an error. This sentence has been removed from the report.

Issue 13 Adjustment for trisomy 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 76, Section 4.9.2: "The EAG notes that trisomy 21 (available in both studies) is considered as an important covariate for adjustment based on Table 21 but it has not been adjusted for by the company."	The sentence should include mention of why trisomy 21 was not adjusted for, as rationalised in the CS. Please consider amending as follows: "The EAG notes that trisomy 21 (available in both studies) is considered as an important covariate for adjustment based on Table 21	The EAG has omitted justification for the exclusion of trisomy from the pooled MAIC analysis provided by the company. As noted in Section B.2.9 of the CS, a balance between precision and clinical relevance was adopted by prioritising higher ranking	We have clarified that ESS was a criterion used to inform covariate selection in the MAIC. The text on page 76 has been amended to read:

	but it has not been adjusted for by the company. **Data on trisomy 21 were not available for the B2101J study, and adjusting for this baseline characteristic would have resulted in an ESS < 50%.**"	characteristics while ensuring sufficient effect sample size of at least 50% of the patient population. This leads to a biased interpretation of the methods used by the company in its analysis.	*"The company selected baseline characteristics to be included in the MAIC based on data availability and input from clinical experts**, as well as making sure the effective sample size (ESS) was at least 50% of the patient population.**"*

Issue 14 Consideration of covariate adjustments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 87, Section 4.10: "The company only considered potential treatment effect modifiers of high importance in the matching."	Please consider amending as follows: "The company considered all potential treatment effect modifiers; however, **treatment effect modifiers were adjusted for according to priority whilst ensuring that the ESS remained >50%, and thus only those of high importance could be included in the matching**"	Balancing the number of covariates adjusted for and the ESS is an unavoidable limitation of analyses of this kind, which has been carefully considered by the company, and should therefore be reflected in the EAG report.	For clarity, we have amended the text on page 87 to read: *"The company only considered potential treatment effect modifiers of high importance in the matching **to achieve a balance between clinical relevance and sufficient ESS.**"*
Page 87, Section 4.10: "In addition, for the potential effect modifiers that are included in the analysis, the company has selected different covariates for the same comparison without sufficient justification. In the comparison against blinatumomab, two covariates	As noted in Section B.2.9, the choice of covariates to be adjusted for was informed by the availability of data in included studies, and the need to maintain sufficient ESS. Not all covariates adjusted for in the ELIANA analysis were available in the ENSIGN and B2101J trials, meaning inclusion in the pooled analysis would have led to ESS		This is not a factual inaccuracy. The EAG does not agree that ESS should be used as a basis for determining which covariates to include in the adjustment model. Excluding relevant prognostic factors and/or treatment effect modifiers from the adjustment model on the basis of low ESS will guarantee that the

were adjusted for when using the pooled tisagenlecleucel data, but six covariates were included in the analysis using ELIANA only.[34] In the comparison against salvage chemotherapy, two covariates were adjusted for when using the pooled tisagenlecleucel data, but three covariates were included in the analysis using ELIANA study."	<50%, and were therefore not adjusted in the pooled analysis. Please consider amending this section of the report accordingly: "In addition, for the potential effect modifiers that are included in the analysis, the company has selected different covariates for the same comparison**, in order to maintain ESS >50% across all analyses**. In the comparison against blinatumomab, two covariates were adjusted for when using the pooled tisagenlecleucel data, but six covariates were included in the analysis using ELIANA only.[34] In the comparison against salvage chemotherapy, two covariates were adjusted for when using the pooled tisagenlecleucel data, but three covariates were included in the analysis using ELIANA study."		underlying assumptions of the unanchored MAIC are not met. The EAG report has not been amended.
Page 89, Section 4.11: "The EAG does not believe that all relevant prognostic factors and treatment effect modifiers have been included and properly adjusted for in the MAIC."	Please consider amending this sentence on the basis that adjusting for all relevant prognostic factors and treatment effects modifiers would lead to a large drop in ESS, and considerably less certain estimates of relative treatment effect.		Please refer to the EAG response above.

Issue 15 Description of model decision tree

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96, Section 5.2.2: "81.4% of patients go on to receive the tisagenlecleucel infusion. These patients subsequently enter into the partitioned survival model. These patients incur 100% of the costs of leukapheresis and bridging chemotherapy costs and 96% of the cost of lymphodepleting chemotherapy."	Please consider amending as follows: "81.4% of patients go on to receive the tisagenlecleucel infusion. These patients subsequently enter into the partitioned survival model. 100% **of these patients are assumed to incur** the costs of leukapheresis and bridging chemotherapy costs and 96% **incur** the cost of lymphodepleting chemotherapy."	The number of patients incurring costs of leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy is based on ELIANA trial data, therefore these suggested descriptions are a more accurate reflection of the model's decision tree element.	The EAG agrees. The text has been amended in line with the company's suggestion.
Page 118, Section 5.2.4: "18.6% of patients in whom tisagenlecleucel is planned do not receive the infusion, due to AEs, manufacturing error or death prior to infusion. The model assumes that all of these patients undergo leukapheresis and 50% of patients receive bridging chemotherapy and lymphodepleting chemotherapy. The costs of leukapheresis are included in the model for these patients."	Please consider amending the description of the decision tree to discuss patients who did not receive tisagenlecleucel due to death separately from those who did not receive tisagenlecleucel due to AEs or manufacturing error, as these incur different costs in the model.		The EAG believes that the description is already accurate. We have slightly modified the text as follows: *"**Regardless of the reason for not receiving the infusion,** the model assumes that all of these patients undergo leukapheresis and 50% of patients receive bridging chemotherapy and lymphodepleting chemotherapy. The costs of leukapheresis are included in the model for these patients."*

Issue 16 Justification for choice of survival curve

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 105, Section 5.2.4: "The EAG notes that the log-normal MCM appears to be more closely aligned with the clinicians' expectations of survival than both the log-logistic and generalised gamma MCMs […]."	Please consider amending as follows: "The EAG notes that the log-normal MCM appears to be more closely aligned with the clinicians' expectations of survival than both the log-logistic and generalised gamma MCMs**, but is less closely aligned with clinicians' estimates of cure** […]."	The reasons for the choice of survival curve should be acknowledged, namely that the predicted cure aligned with clinician estimates of cure.	This is not a factual inaccuracy. As discussed in Section 5.3.5 of the EAG report, the cure fraction is a statistical concept, whereby the survivor function of the MCM asymptotes to the cure fraction at time infinity. The EAG believes it is unlikely that this is how the company's clinical experts expressed their expectations of cure. This is particularly relevant to AFT models (e.g., the log-normal and log-logistic models), whereby some of the non-cured population have a long expected survival. For example, in the company's original base case model, based on the log-logistic model fitted to ELIANA only, 25% of non-cured patients are still alive at 5 years and 13% are still alive at 10 years. Some of these long-term survivors might be considered as cured, despite not being in the cured group of the MCM. The EAG report has not been amended.

Issue 17 Description of health state costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 120, Section 5.2.4: "Unit costs were taken from NHS Reference Costs[77] 2021/22 and the BNF.[79] These costs are assumed to be independent of treatment group; […]"	Please consider amending as follows: "Unit costs were taken from NHS Reference Costs77 2021/22 and the BNF.[79] These costs are assumed to be independent of treatment group **in the case of the PD health state**; […]"	Health state costs are only independent of treatment in the case of the PD health state. Whilst this is clarified elsewhere, this should also be made clear here.	This is not a factual inaccuracy. This paragraph already states twice that these costs are independent of treatment group: *"The follow-up schedule for patients with progressed disease was assumed to be the same for all treatment groups…"* *"These costs are assumed to be independent of treatment group;.."* The EAG report has not been amended.

Issue 18 Utility values from ELIANA for scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 147, Section 5.3.5 "the EAG notes that the executable model applies the utility values from ELIANA for 2 years, with the long-term survivor utility value also based on ELIANA. The EAG is unclear	This statement should be removed.	For the scenario applying utility values from ELIANA for 2 years, it was intended to inform the long-term survivor utility value using estimates from Kelly *et al.* (2015). However, the Company recognises that there was an	This is not a factual inaccuracy – the text reflects the discrepancy between the model and the CS, and the resulting ambiguity about what the company had intended this analysis to reflect. We have amended the EAG report to

whether the company had intended to use Kelly et al. or ELIANA to represent the long-term survivor utility value."		error in the implementation of the scenario in the original model, wherein the long-term survivor utility value is based on ELIANA. The Company apologises for this error, and has updated its most recent base case accordingly, with deterministic results found in the Appendix, Table 1.	exclude the final sentence of the paragraph. The corrected results presented in Table 1 of the appendix to this FAC response are deterministic and use the tisagenlecleucel list price, yet all results in Table 49 of the EAG report are probabilistic and include the tisagenlecleucel PAS price. The EAG has not re-run the results for the corrected analysis.

Issue 19 Clinician estimates of SMR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 146, Section 5.3.5: "The EAG notes that the clinical experts consulted by the company provided a wide range of lower and upper plausible SMRs of 1.5 and 10."	Please consider amending as follows: ""The EAG notes that the clinical experts consulted by the company provided a wide range of lower and upper plausible SMRs of 1.5 and 10, **however estimates of most plausible SMRs ranged from 3.0 to 4.0."**	The EAG has focused on upper and lower plausible estimates of SMR across individual clinicians, and omitted the range of most plausible SMRs reported across clinicians. This overrepresents the spread of answers provided by clinicians, and should be amended to give a better reflection of clinicians' estimates of SMR.	This is not a factual inaccuracy. However, for clarity, the EAG has amended the text as suggested: *"The EAG notes that the clinical experts consulted by the company provided a wide range of lower and upper plausible SMRs of 1.5 and 10**, although their "most likely" estimates suggested a narrower range of 3.0 to 4.0.**"*

Issue 20 Sources of model inputs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 131, Section 5.3.3 "However, the EAG was unable to identify the proportion of patients requiring hospitalisation for lymphodepleting chemotherapy, BSA estimates, outpatient and ICU days to administer tisagenlecleucel, and the cost of idarubicin reported in the CS."	This statement should be revised as follows: "The EAG was unable to verify the following inputs as they were generated from analyses of IPD or pseudo IPD: the proportion of patients requiring hospitalisation for lymphodepleting chemotherapy, outpatient and ICU days to administer tisagenlecleucel, and BSA estimates"	As noted in the CS Section B3.5.1, the proportion of patients requiring hospitalisation for lymphodepleting chemotherapy was based on the analysis of hospitalisation data from the ELIANA trial. Similarly, length of hospitalisation stay for tisagenlecleucel was based on individual patient data (IPD) from the ELIANA trial. BSA estimates were also calculated from IPD, using the Mostellar formula. At the time of submission, the cost of idarubicin was derived based on latest estimates from the BNF website, which has since been updated.	This is not a factual inaccuracy. The EAG was unable to find these values in the CS or the CSRs. Some inputs were reported in the CSRs, whilst others were not. For the sake of clarity, the following sentence has been added to the EAG report: *"During the factual accuracy check, the company clarified that the cost of idarubicin used in the model could not be identified by the EAG because this unit cost was updated in the BNF after the CS was submitted to NICE."* The EAG notes this is a minor issue.

Issue 21 Description of company MAICs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 166, Section 5.7: "Given the problems in the company's MAICs, the	Please consider using more neutral language when describing the company MAICs:	The company considers that the EAG's description of the company MAIC analyses may	In this context, the EAG believes the terms "limitations" and "problems" are synonymous.

company's economic model is based on naïve ITCs between tisagenlecleucel and its comparators."	"Given the **limitations** in the company's MAICs, the company's economic model is based on naïve ITCs between tisagenlecleucel and its comparators."	misrepresent the unavoidable limitations of unanchored population-adjusted analyses as methodological errors.	However, the text has been amended, as suggested.

Issue 22 Description of MCM analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 166, Section 5.7: "The company's use of survival analyses in the economic model is restricted to MCMs only. These models force the distribution to include a cure fraction, which may result in unstable or unreliable parameter estimates if the duration of study follow-up or the number of observed events is insufficient."	Please consider amending as follows: "The company's use of survival analyses in the economic model is restricted to MCMs only. These models force the distribution to include a cure fraction, which **in the case of the comparator studies** may result in unstable or unreliable parameter estimates if the duration of study follow-up or the number of observed events is insufficient."	Whilst the company agrees with the EAG's interpretation of the limitations associated with MCMs, the company believe that this largely applies to the comparator studies included in the model, given the maturity of the latest ELIANA trial data (where a plateau has been clearly demonstrated, and where cure parameter estimates were generally consistent across models explored).	This is not a factual inaccuracy. It is a general point which applies to fitting mixture-cure models to data from any study. There is no formal statistical test to determine whether follow-up is sufficient to fit mixture-cure models (see Othus *et al.*, Value in Health, 2020, vol. 23). The EAG agrees that the problem of limited follow-up is more prominent for the blinatumomab and salvage chemotherapy studies; however, it is not accurate to suggest that it does not also apply to the tisagenlecleucel data. The EAG notes that for OS, the estimated cure fractions fitted to the pooled dataset are not fully consistent as they range from 22% to 43%. Similarly, for OS in

			ELIANA, the cure fractions range from 33% to 53%.

Issue 23 Description of RCS analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 166, Section 5.7: "The EAG believes that it would have been useful to explore the use of alternative flexible models, such as RCS distributions, combined with a structural assumptions of a cure timepoint."	Please consider amending this sentence to reflect the fact that any such analysis would rely on potentially arbitrary assumptions around a cure timepoint and proportion.	Whilst they are subject to limitations, MCMs ensure the prediction of a cure fraction is based on the available data and reflect the theoretical basis of a cure for a proportion of patients. The corresponding limitations of alternative analyses suggested by the EAG should be noted for accurate comparison of the merits of each approach.	This is not a factual inaccuracy. It is already stated that this approach would require structural assumptions of a cure timepoint. However, that does not mean that the assumptions would be arbitrary - they should be based on clinical plausibility. A range of cure timepoints could have been assessed, had this approach been used. The EAG report has not been amended.

Section 2: Errors in reporting of data

Issue 24 Maximum total dose of tisagenlecleucel in B2101J trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 41, Table 6, Section 4.2.2: "Maximum total dose of 1.5×107 to 5×109 […]"	Please amend as follows: "Maximum total dose of 1.5×10^{7} to 5×10^{9} […]"	The description of maximum total dose in the B2101J trial has accidentally omitted scientific notation.	The EAG agrees. The text has been amended as suggested.

Issue 25 Maximum total dose of tisagenlecleucel in B2101J trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, Table 8, Section 4.2.4; **Karnofsky/Lanksy performance status, n (%)** / **ELIANA (N=79)** 60 or less / 5 (7)	Please amend as follows: Karnofsky/Lanksy performance status, n (%) / ELIANA (N=79) 60 or less / 5 (**6**)	The percentage of patients with Karnofsky/Lanksy performance status of 60 or less has been incorrectly rounded.	The EAG agrees. The text has been amended as suggested.

Issue 26 Original company base case ICER

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Page 164, Table 56, Section 5.6;
<table>
<tr><th>Scenario</th><th>Weighted ICER: Tisagenlecleucel vs blinatumomab</th></tr>
<tr><td>Company’s original base case, deterministic</td><td>£11,305</td></tr>
</table>
</td>
<td>Please amend as follows:
<table>
<tr><th>Scenario</th><th>Weighted ICER: Tisagenlecleucel vs blinatumomab</th></tr>
<tr><td>Company’s original base case, deterministic</td><td>£11,304</td></tr>
</table>
</td>
<td>The base case deterministic CER for tisagenlecleucel versus blinatumomab has been misreported.</td>
<td>The EAG agrees. The ICER has been amended as suggested.</td>
</tr>
</table>

Additional note: The post-FAC version of the EAG report includes a number of very minor editorial corrections, formatting changes and changes in the redaction of confidential information.

Appendix

Table 1. Updated scenario analysis results based on corrections applied as per Issue 5(tisagenlecleucel list price; no severity modifier applied)

#	Scenario	Versus blinatumomab				Versus salvage chemotherapy			
		Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
0	Base case*	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]
1	Issue 5: ELIANA PFS and PD utility for two years, with long-term survivor utility based on Kelly et al.	[redacted]	7.10	[redacted]	[redacted]	[redacted]	8.15	[redacted]	[redacted]

Abbreviations: EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PD: progressed disease; QALYs: quality-adjusted life year
Footnote: *This is the updated Company base-case based on the revised model submitted as part of the response to clarification questions from the EAG

References

1. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554) [ID6290]: Final scope. Available at: https://www.nice.org.uk/guidance/gid-ta11381/documents/final-scope-2. [Last accessed: 16 August 2023]. 2023.
2. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010;376:2009-2017.
3. Kelly MJ, Pauker SG, Parsons SK. Using nonrandomized studies to inform complex clinical decisions: the thorny issue of cranial radiation therapy for T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer. 2015;62:790-7.