NICE 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 [ID1167]

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 [ID1167]

Contents:

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

Pre-meeting briefing

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report
- comments received as part of the technical engagement

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Abbreviation	In full
AE	Adverse events
ALL	Acute lymphoblastic lymphoma
Allo-SCT	Allogenic stem cell transplantation
BNF	British National Formulary
CAR	Chimeric antigen receptor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRS	Cytokine release syndrome
DOR	Duration of response
EFS	Event-free survival
EQ-5D	EuroQol five dimensions questionnaire
ERG	Evidence review group
HGG	Hypogammaglobulinaemia
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
IVIG	Intravenous immunoglobulin

Abbreviation	In full
KM	Kaplan—Meier
LYG	Life years gained
MRD	Minimal residual disease
NE	Not evaluable
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NR	Not recorded
ORR	Overall remission rate
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
Ph+	Philadelphia chromosome positive
Ph-	Philadelphia chromosome negative
QALY	Quality-adjusted life year
RFS	Relapse-free survival
SAE	Serious adverse event
SCT	Stem cell transplant
TKI	Tyrosine kinase inhibitor
Tis-T	Tisagenlecleucel-T

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Key issues – clinical effectiveness

- Would the following populations be treated with tisagenlecleucel -T (tis-T):
  - patients with primary refractory ALL,
  - patients with Philadelphia chromosome positive ALL.
  - patients previously treated with anti CD-19 therapies (e.g. blinatumomab)
- Is it appropriate to use clofarabine as a proxy for FLA-IDA salvage chemotherapy?
- Is blinatumomab an appropriate comparator?
- Are the patient populations in the clinical evidence generalisable to NHS clinical practice?
- Which studies are appropriate to use as clinical evidence for the comparators?
- Is there sufficient evidence that tis-T should be considered a curative therapy?
- Should efficacy analysis include the entire ITT population?

Key issues – cost effectiveness

- Is it valid to assume a curative effect for tis-T (and comparators) in the model?
- Is blinatumomab an appropriate comparator?
- What is the most appropriate comparator data source for salvage chemotherapy?
- What is the most appropriate overall survival extrapolation?
- Addressing other uncertainties in the model:
  - Prevalence and duration of B-cell aplasia
  - Prevalence of stem-cell transplants
- Are the end of life criteria met?
- Should the 1.5% discount rate be applied?

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Acute lymphoblastic leukaemia (ALL): Disease background

- Acute form of cancer of the white blood cells
- Rare - 0.2% of new cancers in UK
- Predominately disease of childhood but affects adults too
- Symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- 64% of cases of ALL in patients aged 0–24 years
- Precursor B-cell is the most common type of ALL representing 80–85% of cases in children
- Approximately 3% of children with precursor B-cell ALL have acquired chromosomal abnormality known as Philadelphia chromosome positive disease – which is associated with a poorer prognosis and is challenging to treat

Acute lymphoblastic leukaemia (ALL): Disease background

- Currently no NICE clinical guidelines on treatment of ALL
- NICE technology appraisal guidance for ALL includes:
  - TA 408: pegaspargase is recommended for untreated ALL in children, young people and adults
  - TA 450: blinatumomab is recommended for treating Philadelphia-chromosome-negative relapsed or refractory precursor B-cell ALL in adults (funding extended to children by NHS England)
  - TA 451: ponatinib is recommended for treating Philadelphia-chromosome-positive ALL in adults under certain conditions
  - Final appraisal document (FAD) for appeal [ID893]: Inotuzumab ozogamicin is recommended, for treating relapsed or refractory CD22- positive B-cell precursor acute lymphoblastic leukaemia in adults

No NICE guidelines in ALL. EMSO Guidelines:

Ann Oncol. 2016 Apr 7. pii: mdw025 Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C; ESMO Guidelines Committee.

Full ponatinib recommendation:

Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia-chromosome-positive acute lymphoblastic leukaemia in adults when:

the disease is resistant to dasatinib or

they cannot tolerate dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate or

the T315I gene mutation is present.

Tisagenlecleucel-T (Novartis)

Mechanism of action	A chimeric antigen receptor (CAR) T-cell therapy that uses autologous T cells engineered to express a novel surface receptor directed against the tumour antigen CD19

Administration and dosage	• Patients T cells are extracted via leukapheresis
	• Patients are administered lymphodepleting chemotherapy of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV (cytarabine and etoposide may be used if cyclophosphamide treatment is not suitable)
	• Genetically altered T cells are administered as a single dose intravenous infusion 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)

Marketing authorisation	Received positive CHMP opinion (June 2018) 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
List price	£282,000
PAS	Simple discount under discussion with NHS England

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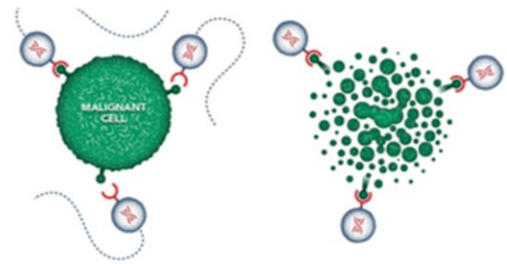
Source: Company submission table 2, p16-19

Chimeric antigen receptor (CAR) T-cell therapies

- Tisagenlecleucel (tis-T) is the first chimeric antigen receptor (CAR) T-cell therapy for ALL to be appraised by NICE for use in the NHS
- CAR T-cell therapies employ an inactive virus to insert genes into autologous human T cells.
- The engineered T cells express a novel cell surface receptor fragment antibody.
- The new receptors identify and lock onto CD19 bearing cells.
- Once locked onto CD19 the T cell is activated to destroy the cells.
- Tis-T includes costimulatory domain to increase T-cell activation and enhance antitumour function



CAR recognises targets on surface of malignant cell

CAR T cells destroy the malignant cells

Source: Adapted from figure 2 in company submission

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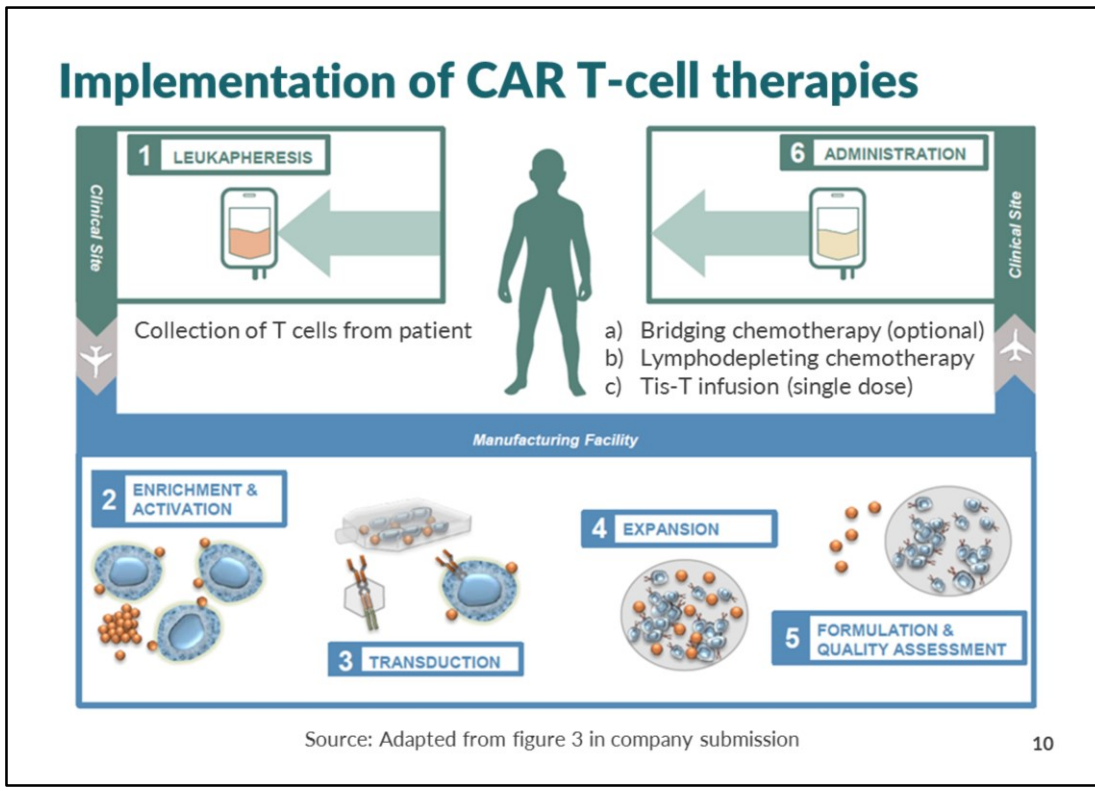
CAR T-cell therapy:

Engineered Autologous Cell Therapy is a process by which a patient's own T-cells are collected and genetically altered to recognise and target antigens expressed on the cell surface of specific malignancies. (Source: Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015; 33(6):540-9.)



Source; company submission, table 2 page 18:

Step 1: The patient is admitted to hospital and their mononuclear cells are obtained by a process known as leukapheresis.

Step 2: The patient's cells are then cryopreserved in the vapour phase of liquid nitrogen and shipped to a manufacturing facility in the US using a dedicated courier service.

Step 3: At the manufacturing facility, the mononuclear cells are thawed and enriched for T cells. The T cells are activated with antibody-coated beads and genetically transduced using a lentiviral vector (inactive virus) containing the anti-CD19 CAR transgene.

Step 4: The CAR-T-cells then undergo ex vivo expansion on antibody-coated beads

Step 5: The CAR-T-cells undergo formulation and a strict quality assessment before being released, cryopreserved and shipped. As an autologous (patient specific) product entering the EU, each individual therapy then requires a separate certification and batch release appropriate to the European regulations governing genetically modified advanced therapy medicinal products. Following certification, the product is sent back to the hospital where it can be stored in liquid nitrogen for up to 9 months until

the treating centre / staff are ready to administer, and the patient is ready to receive treatment.

Step 6: The patient can receive bridging chemotherapy between leukapheresis and infusion at the discretion of the treating physician. Prior to tisagenlecleucel infusion the patient receives a preparative low dose lymphodepleting regimen. The CAR-T-cells are then thawed and reinfused into the patient as a one-time single-dose of tisagenlecleucel.

Summary of patient and professional group comments

- There is unmet need for new treatments for ALL in the relapsed refractory setting
- CAR T-cell therapy is a novel treatment and has the potential to change the treatment pathway
  - Treatment would be offered with curative intent
- Significant infrastructural changes will be required to deliver CAR T-cell therapy routinely in the NHS
  - Manufacturing, delivery of treatment and management of side effects must be considered

Comments from patient groups

ALL and current treatment:

- Common symptoms encountered by patients are: tiredness, bruising, bleeding, infections and weight loss. Other symptoms include swollen lymph nodes, stomach pain, bone pain and night sweats
- Effective treatment options are limited in the relapsed setting. Side effects of chemotherapy include fatigue, nausea/sickness, infections, bleeding, organ dysfunction and hair loss

CAR-T treatment:

- Treatment with CAR T-cell therapy can offer hope at a time when all other options have failed
- Patients who have responded to treatment in clinical trials have had exceptionally good results
- A patient noted although treatment was intense it was less draining that chemotherapy and the inconvenience of this period was insignificant when compared with the possibility that they would respond well to the treatment and ultimately be cancer-free

Implementation:

- Treatment is intensive and requires patients to be admitted and/or stay in ambulatory care close to the hospital for several weeks – placing strain on patients, families and carers

Comments from professional groups

Current treatment options:

- Clear unmet need for patients who have disease that is unresponsive to conventional therapy
- Patients who relapse after allo-SCT or are refractory to conventional chemotherapy have an extremely poor prognosis

CAR –T cell therapy:

- The technology is a game changer in the way leukaemia (and possibly other cancers) will be treated in future
- All post allograft relapse would be treated with curative intent
- Once established, will improve access to the treatment in the UK and remove the need for patients to go abroad to receive it.

Implementation:

- Centres will need to demonstrate [...] that they have the facilities and experience to administer CAR T cells and its complications (CRS, neurology etc
- Investment will be required to expand existing infrastructure for collecting, freezing, transporting and receiving these gene modified cells. Some investment will also be required in creating extra high dependency and intensive care bed capacity.

Statement from NHS England (1)

- As an innovation in personalised medicine, this technology has the potential to revolutionise current treatment strategies … Although the allogeneic stem cell transplant pathway will provide some guidance, the technology will require new pathways for the preparation of patients, manufacture of the medicine, delivery of the medicine and long-term monitoring of the patient
- [It] will require a new service specification
- Severe, life threatening, adverse events are not uncommon and this will have an impact on the pathway, requiring an increase in intensive care support compared to the current pathway. The paramount focus on safety is likely to necessitate 'ramp-up' access over a period of time to allow for manufacturing and care delivery capacity to develop. This will include manufacturer to NHS provider contracting, ongoing training, ongoing accreditation, assured access to ITU capacity etc.
- Due to the novelty of the treatment and the logistics involved, all key stakeholders have indicated the need for a phased implementation if approved. This is likely to mean that geographical access at the start will be worse than current access to chemotherapy/HSCT. It is expected that this would be redressed over time as experience and capacity improves"

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Source: statement from NHSE specialised commissioning

Statement from NHS England (2)

Treatment pathway

- Current standard treatment for disease refractory to 1st line induction in those aged less than 18 years is mainly using the NOPHO protocol
  - Comparator for 1st line refractory patients should be mainly the NOPHO protocol (blinatumomab used in young adults)
  - Tis-T trials excluded patients previously treated with blinatumomab → no evidence of the efficacy of tis-T in patients previously treated with blinatumomab
- No biologically plausible reason for Ph+ patients not to be treated with tis-T, such patients were included in trials (although patient numbers small)
- Inotuzumab ozogamicin is likely to rapidly displace much use of blinatumomab and especially so in the relapsed/refractory ALL population
- The one definite comparator in the right place in the treatment pathway for the appraisal of tis-T is combination chemotherapy

Salvage chemotherapy comparator data

- Clofarabine monotherapy data old → outcomes likely to be inferior to more contemporary use of FLA-IDA → use of clofarabine data as proxy for FLA-IDA inappropriate

Adverse events

- Until long-term data are available, a pragmatic estimate of IVIG treatment for B-Cell aplasia of up to 50% of responders for a period of 12-24 months would not be unreasonable

IVIG, intravenous immunoglobulin; Ph+, Philadelphia chromosome positive

Source: statement from clinical lead for CDF

Statement from NHS England (3)

Rates of stem cell transplant and overall survival for comparators

- Expert opinion to NHS England indicates that there were extended times to SCT in the TOWER blinatumomab trial and thus the SCT for blinatumomab is expected to be higher than 24% and thus the long term OS rate is likely to be about 15-18%.
  - However, position of blinatumomab in the treatment pathway is likely to change
- Expert opinion to NHS England indicates the SCT rate for salvage chemotherapy is likely to be 15-20% and the long term OS rate about 10%.

Comments on the company's economic model

- The costs of patients having to remain close to treating centres need to be included in the economic analysis
- Hospital costs are challenging to estimate therefore a scenario analyses using the inpatient and follow up costs of a related service such as an allogeneic SCT for an unrelated donor, would offer a useful analysis to compare with the company and ERG's base case assumptions of hospital cost

Cancer Drugs Fund

- Depending on the NICE committee's conclusions as to clinical and cost effectiveness, NHS England regards tis-T as a good candidate for the Cancer Drugs Fund as the EFS and OS results are still not mature. An extra 12 months of follow-up and up to date analyses of the trials would significantly reduce this uncertainty

EFS, event-free survival; OS, overall survival; SCT, stem-cell transplant

Source: statement from clinical lead for CDF

Decision problem (1)

	NICE scope	Company
Population	People aged 3 to 25 years with relapsed or refractory B-cell ALL	In line with anticipated marketing authorisation: 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*
Outcomes	• Overall survival (OS) • Event-free survival (EFS) • Relapse-free survival (RFS) • Response rate (including minimal residual disease [MRD], haematological responses and complete remission [CR]) • Rate of allogenic stem cell transplant (allo-SCT) • Adverse effects of treatment • Health-related quality of life	

*Company noted that as a result of a lack of data in the Philadelphia chromosome positive population it was not feasible to perform a robust comparison for this subgroup

Source: Company submission, table 1, p12-15

Decision problem (2)

	NICE scope	Company

Comparators	Established clinical management without Tis-T at following lines:
	• Bone marrow relapse
	  • 2nd or later relapse
	  • Relapse within 6 months of allo-SCT
	• Primary refractory disease
	• Philadelphia chromosome +ve ALL
	  • Intolerant/contraindicated to tyrosine kinase inhibitors (TKIs)
	  • Failed 2 TKIs
	  • Ineligible for allo-SCT
		• Salvage chemotherapy (specifically, FLA-IDA [fludarabine, cytarabine and idarubicin])
		• Blinatumomab
		
		The above are stablished clinical practice at following lines:
		• Bone marrow relapse
		  • 2nd or later relapse
		  • Relapse within 6 months of allo-SCT
		• Primary refractory disease

Company rationale for difference from scope	• Ph+ ALL <3% of eligible population → TKIs not relevant comparators • No comparison for Ph+ population presented due to lack of available data for Tis-T and relevant comparators	

ERG comments: Clinical advice to ERG stated blinatumomab increasingly used after first relapse → FLA-IDA main comparator

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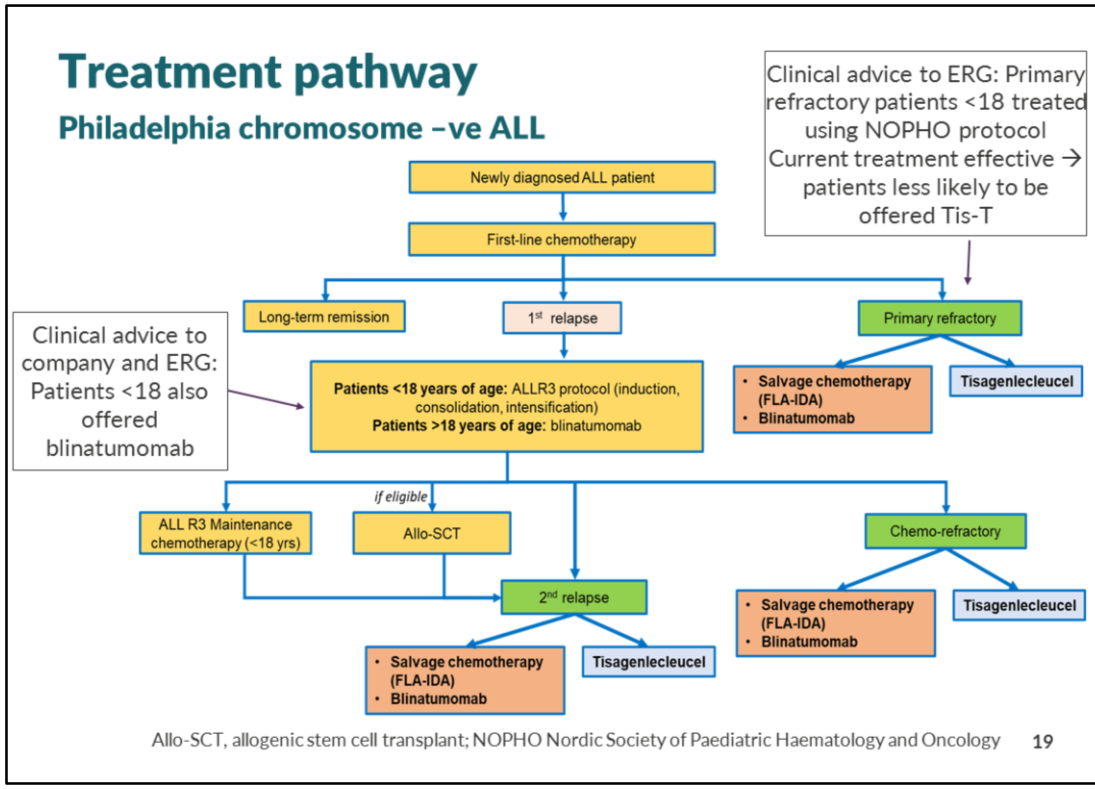
Source: Company submission, table 1, p12-15



Sources: company submission, p24-25, figure 6, ERG report pages 28-29

Notes:

Company submission states: No NICE clinical guideline, ESMO guideline doesn't specify a specific choice of treatment for relapsed/refractory ALL. ERG report notes that there are (unpublished) guidelines by the Childhood Leukaemia Clinicians Network (CLCN).

Company states in submission that

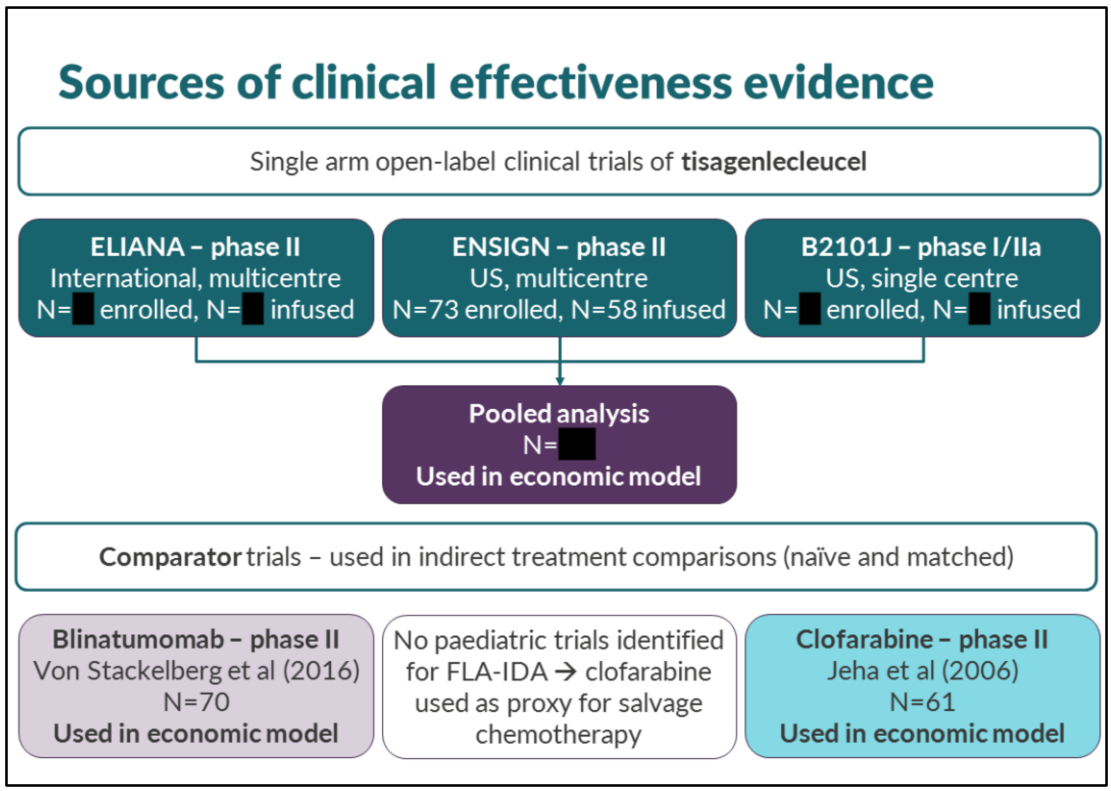
Approx 20% of patients experience relapse after first-line chemotherapy

Clofarabine is licensed for second relapse – company states feedback from clinicians suggest it is rarely used.

Pathway for Ph +ve ALL not shown. Patients treated with tyrosine kinase inhibitors. Patients had to have failed 2 lines of TKI to be eligible for tisagenlecleucel trials. ESMO guidelines for treatment of

Ph+ ALL are available at https://academic.oup.com/view-large/35557775

Clinical effectiveness



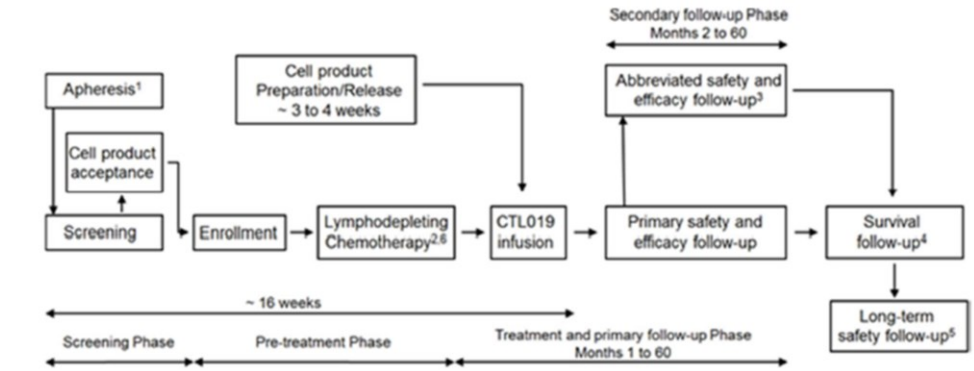
Source, company submission table 3, p28, and p66-69

Notes:

Matching indirect comparison used as scenario analysis (naïve comparison used in model

Alternative studies identified for comparators were used in scenario analyses

ELIANA – study design



Patients

- Age 3 at screening to age 21 at initial diagnosis
- Relapsed/refractory ALL with 2 or more relapses or relapse after allo-SCT or primary/chemo refractory ALL or Ph+ve ALL if TKI failed/contraindicated
- Kamofsky/Lansky performance status ≥50

Endpoints

1°

- Overall remission rate (independently-assessed)

2° endpoints used in model

- Overall survival
- Event-free survival
- Adverse effects of treatment

Source: Company submission page 29-32 (study design diagram from figure 7)

Notes:

Other secondary endpoints in ELIANA include:

ORR (best overall response [BOR] of CR or CRi) with MRD negative bone marrow

DOR

RFS

Patient-reported outcomes

ORR determined by IRC assessment (defined as a BOR of either CR and 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

ENSIGN and B2101J trials

- Study design similar, key differences between trials include:
  - Leukapheresis could occur prior to or after enrolment in B2101J (patients were enrolled following leukapheresis in ELIANA and ENSIGN)
  - Some patients with lymphoma eligible in ENSIGN and B2101J – no data for patients with lymphoma presented (in line with ELIANA)
  - B2101J was a dose escalation study → patients could receive up to 3 doses of tisagenlecleucel-T
  - Median duration of follow up at latest data cuts was
    - ELIANA: [redacted]
    - ENSIGN: 19.6 months
    - B2101J: [redacted]

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Source: company submission p27, p33-37, table 4

Selected baseline characteristics

Characteristic	ELIANA (full analysis set) (N=[redacted])	ENSIGN (full analysis set) (N=58)	B2101J (full analysis set) (N=[redacted])
Age (years), median (range)	[redacted]	12.0 (3–25)	[redacted]
Male, n (%)	[redacted]	27 (46.6)	[redacted]
Karnofsky/Lansky performance status, n (%)			
100	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]
60, 50 or <50	[redacted]	[redacted]	[redacted]
Prior haematopoietic stem cell transplant (SCT)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Primary refractory	[redacted]	5 (8.6)	[redacted]
Philadelphia chromosome +ve	[redacted]	[redacted]	[redacted]

ERG's comments:

- Differences in performance status, number of patients without SCT and proportion with primary refractory disease
- Company presented baseline data for infused patients only rather than full intention-to-treat (ITT) population
  - **Fewer patients with performance status 100 in full ITT population**

Source: Adapted from company submission table 6, p40-41, ERG report p37

Ph+ve proportion from company response to clarification, p5-6

Trial results – summary of individual trials

n (%) Patients receiving infusion only	ELIANA (N=[redacted]) (N=[redacted] for ORR and DoR)	ENSIGN (N=58) (N=42 for ORR and DoR)	B2101J (N=[redacted])
Primary efficacy results			
ORR (CR+CRi) (95% CI; p value)	[redacted]	29 (69.0) (52.9, 82.4; <0.0001)	[redacted]
CR	[redacted]	27 (64.3)	[redacted]
CRi		2 (4.8)	
NR		9 (21.4)	
Unknown		4 (9.5)	
ORR with bone marrow MRD negative (95% CI)	[redacted]	27 (64.3) (48.0, 78.4)	[redacted]
Secondary efficacy results			
Duration of response (/Relapse-free response)			
% event free at 12 months (95% CI)	[redacted]	61.2 (37.8, 78.0)	[redacted]
Median (months) (95% CI)		NE (5.9, NE)	
Event-free survival (used in economic model)			
% event free at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
Median (months) (95% CI)			
Overall survival (used in economic model)			
% at 12 months (95% CI)	[redacted]	62.6 (45.8, 75.6)	[redacted]
Median (months) (95% CI)		23.8 (8.8, NE)	

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DoR, duration of response; MRD, minimal residual disease; NE, not evaluable; ORR, overall remission rate.

Source: Company submission table 11, p47-48

Notes:

MRD negative status defined as MRD less than 0.01%. MRD status is a prognostic factor for relapse and MRD negative status a marker of deep remission.

As with baseline characteristics ERG notes that these results are on infused population only and not the entire intention-to-treat population

Pooled trial results – event-free survival

Data cuts: ELIANA, Dec 2017; ENSIGN, Oct 2017; B2101J, Jan 2017
CI, confidence interval; NR, not recorded

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Source: Company submission page 64-65, figure adapted from figure 21

Pooled trial results – overall survival

Data cuts: ELIANA, Dec 2017; ENSIGN, Oct 2017; B2101J, Jan 2017
CI, confidence interval; NR, not recorded; OS, overall survival

ERG: Small number of patients at risk after 38 months → interpret median OS with caution

Source: Company submission page 64-65, figure adapted from figure 21. ERG report p50

Health-related quality of life

- Patient-reported outcomes collected in ELIANA only
  - Collected for patients ≥8 years old
  - Used PedsQL and EQ-5D questionnaires

Source: Figure 13 of company submission

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Source: company submission p52-53, figure 13

Notes:

EQ-5D-3L questionnaire used for patients aged 13 and above, EQ-5D-3Y (adapted questionnaire for younger patients) used for patients between 8 and 12 years old

Adverse events (AEs) – summary

	ELIANA (safety set) (N=[redacted])	ENSIGN (safety set) (N=58)	B2101J (safety set) (N=[redacted])
Median duration of follow up (months)	[redacted]	19.6	[redacted]
Patients with at least one AE, n (%)	[redacted]	[redacted]	[redacted]
Suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Death within 30 days post-tisagenlecleucel infusion	[redacted]	[redacted]	[redacted]
Death >30 days post-tisagenlecleucel infusion	[redacted]	17 (29.3)	[redacted]
Patients with serious or other significant events, n (%)			
Serious adverse event (SAE)	[redacted]	45 (77.6)	[redacted]
SAE suspected to be study drug-related	[redacted]	42 (72.4)	[redacted]
Grade 3/4 AE	[redacted]	[redacted]	[redacted]
Grade 3/4 AE suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Cytokine release syndrome (CRS), n (%)			
Patients with CRS	[redacted]	47 (81.0)	[redacted]
% of CRS events at grade 3/4	[redacted]	19 (32.7)	[redacted]

ERG: Requested data on B-cell aplasia (absence of B-cells). Company provided pooled data from ELIANA and ENSIGN showed [redacted] probability of recovery at both 12 and 24 months → long-term follow-up needed to assess late effects of B-cell aplasia

Source: Company submission p27, p73-74 (table 21), p83-84, ERG report p52

ERG's comments – tis-T clinical evidence

- Generalisability to NHS clinical practice:
  - Trials restricted to patients with life expectancy >12 weeks → patients in trial may be healthier/have higher performance status
  - Unsure if tisagnelecleucel-T would be offered to patients with primary refractory ALL → population broader
- Clinical outcomes used in model apply to infused patients only, not the full intention-to-treat population → excludes patients who may have poorer prognosis or have benefited from salvage chemotherapy
- Patients previously treated with anti-CD19 therapies excluded from trials → effectiveness after blinatumomab treatment uncertain
- Insufficient follow-up to determine if treatment curative – clinical experts suggest at least 5 years of follow-up required
- [redacted] of patients had an allo-SCT after infusion: company stated in response to clarification that some clinicians chose to consolidate response with allo-SCT, whereas allo-SCT would only be an option in the UK for patients who relapse

SCT, stem cell transplant; tis-T, tisagenlecleucel-T

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ERG report p37-38, 41-51

ERG's comments – manufacturing time

- Manufacturing time important given short life expectancy of patients (between 3 and 9 months) and pace of disease progression → requested median time between enrolment and infusion
- Company: median time between enrolment and infusion in ELIANA, ENSIGN and B2191J was [redacted] days, 41 days and [redacted] days
  - Changes to streamline process lead to manufacturing time of 3-4 weeks, recent data on throughput time of commercial orders report median time of 23 days (range, 21–37 days)
- ERG: Range exceeds pre-specified time of 3-4 weeks
  - Manufacturing time may take significantly longer than 3-4 weeks

31

Source, ERG report p37-39

Comparator clinical evidence – blinatumomab

- Tis-T trials single arm studies so comparator efficacy data drawn from historical cohorts identified by systematic literature review
- Company used evidence from von Stackelberg (2016)
  - Study in patients <18 years with relapsing/refractory B-Cell ALL (n=70)
  - Company stated feedback from experts suggested trial population fitter than those in the tisagenlecleucel trials based on proportion of refractory patients and patients with >3 lines of therapy

ERG's comments:

- Clinical expert feedback suggests blinatumomab would most likely be offered after first-relapse → may not be an appropriate comparator for tis-T
- Population considered was very high risk based on tumour load, multiple prior relapses and short interval between latest treatment and start of blinatumomab → outcomes could be worse than would be expected for blinatumomab
- Median overall survival of 7.5 months in von Stackelberg lower than the overall survival of 9.9 months reported for the age 18–35 subgroup (n=123) in TOWER study of blinatumomab

32

Source: Company submission p66, 70. ERG report p52-53

Comparator clinical evidence – FLA-IDA (1)

- No clinical trials identified by company's systematic review for FLA-IDA
- Clofarabine monotherapy/combination therapy used as proxy for efficacy of FLA-IDA
  - Studies chosen which aligned with expert feedback that median overall survival with FLA-IDA after 2nd relapse would be around 3 months
  - Studies with combination therapies excluded
  - Jeha (2006) matched criteria and used in York regenerative medicines report, Hettle (2017) → considered most appropriate study by company

ERG comments:

- No evidence provided to support equivalency of FLA-IDA and clofarabine
- Excluding trials on the basis of being part of combination therapy not justified
  - Company provided scenario analysis based on 2 of these studies (Hijiya, 2011 and Locatelli, 2009) in response to clarification
- Significant differences in study design and baseline characteristics compared with the tisagenlecleucel trials (eg lower proportion of patients with prior allo-SCT)
- Care may have improved since 2006 when Jeha study was carried out
- **"Comparing theses studies would produce unreliable results"**

SCT, stem cell transplant

Source: Company submission p67-70. ERG report p53-55

Comparator clinical evidence – FLA-IDA (2)

- ERG identified 2 further studies providing evidence for efficacy of FLA-IDA published subsequently to the company's systematic literature review
- ERG notes these studies have larger sample size and longer follow up than studies identified by the company → considers these studies more appropriate and reliable
- Kaplan—Meier curves unavailable for Sun → not suitable for use in model
  - Population more aligned with tis-T than Kuhlen, results supportive of Kuhlen

Sun (2017) – retrospective analysis
N=325, study duration 8 years
Patients ≤21 years old with B-cell ALL: after primary induction failure, or with ≥2 occasions of relapsed disease; or failure to achieve remission ≥1 salvage treatment attempts.
Similar baseline characteristics to tis-T studies
Complete remission rate: 51±3.9% after 2nd salvage attempt, <40% after 3rd/subsequent attempts

Kuhlen (2017) – retrospective analysis
N=242, median follow up 3.4 years
Paediatric patients with B-Cell ALL in 1st relapse after allo-SCT
Similar baseline characteristics to tis-T studies (higher proportion of patients with allo-SCT may underestimate overall survival)
Overall survival after 3 years: 20%
Event-free survival after 3 years: 15%

SCT, stem cell transplant; tis-T, tisagenlecleucel-T

Source:. ERG report p54-55

ERG's critique of FLA-IDA evidence

- ERG prefer use of Kuhlen 2017 for FLA-IDA but note several limitations, which tend to favour tis-T:

Limitation	Direction of bias
All patients have received allo-SCT compared with [redacted] in tis-T trials	Patients who relapse following SCT tend to have a worse prognosis → underestimates OS
A proportion of the patients included (25%) received only palliative care	Patients receiving palliative care will not become long term survivors → underestimates OS
Includes patients with T-cell ALL (subgroup analysis of EFS reported)	Patients with T-cell ALL have a poorer prognosis → underestimates OS
Includes patients who have relapsed within 6 months of SCT, these patients would not be eligible for tis-T (subgroup analysis of EFS reported)	Patients who relapse soon after SCT have a poorer prognosis → underestimates OS
Includes a higher proportion of patients in first relapse than the tis-T trials (29% vs [redacted]; data available for B2101J only)	Patients in first relapse have a better prognosis → overestimates OS
Includes patients with extramedullary relapse (20%) who were not included in tis-T trials	Patients with extramedullary relapse have a better prognosis → overestimates OS

EFS, event-free survival, OS, overall survival; tis-T, tisagenlecleucel-T; SCT, stem cell transplant.

Source: ERG report p82, table 7, final limitation identified by company in factual accuracy check

Indirect treatment comparisons

Adjustment scenario	Naïve comparison		Matched-adjusted indirect comparison	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Tisagenlecleucel vs blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Tisagenlecleucel vs salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Blinatumomab overall survival

Salvage chemotherapy overall survival

ERG: Several key prognostic characteristics not adjusted → populations may still be substantially different. Impact of this uncertainty on survival estimates unknown

Source, company submission p66-71 (table 20, figures 23 and 24). ERG report p56

Notes: Shaded regions represent 95% confidence intervals

Clofarabine efficacy used as a proxy for FLA-IDA salvage chemotherapy efficacy

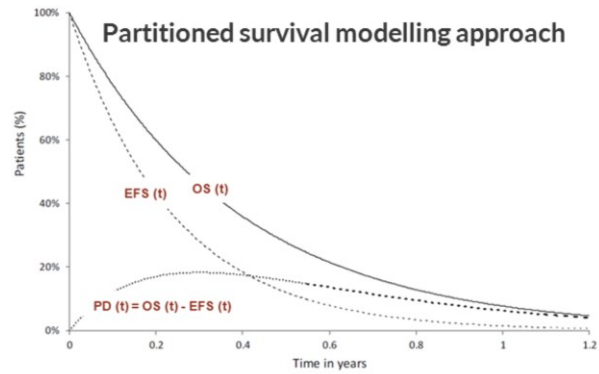
Hazard ratios from indirect treatment comparisons are not used in the economic model. Scenario analysis conducted by the company using the matched-adjusted population had a relatively small effect on the incremental cost effectiveness ratios compared with the company base case (increases ICER vs salvage chemo by around £2,000, decreases ICER vs blinatumomab by £3,000).

Cost effectiveness

Cost effectiveness results

- All incremental cost-effectiveness ratios (ICERs) quoted are based on analyses using patient access scheme price of tis-T
- Blinatumomab (comparator) and tocilizumab (used to treat adverse events of tis-T treatment) have confidential PAS discounts therefore cost effectiveness results including these discounts are included in a confidential appendix

Company's model (1)



- **Partitioned survival model** with 3 states:
  - Event-free survival (EFS)
  - Relapsed/progressed disease (PD)
  - Death
- Patients in tis-T arm move through additional decision tree before entering portioned survival model (see next slide)

- Time horizon: 88 years
- Cycle length: 1 month
- Discount rate: 3.5%
- Clinical inputs based on pooled trial data for tis-T and indirect treatment comparisons for blinatumomab and salvage chemotherapy

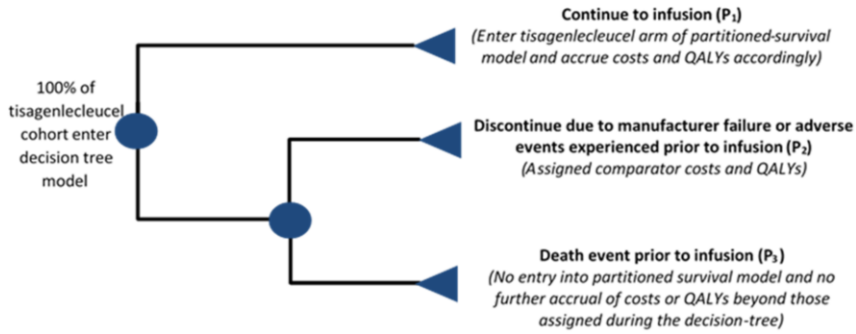
OS, overall survival; tis-T, tisagenlecleucel-T

39

Source: Company submission p93-98 (figures 25 and 26, table 26))

Company's model (2)

- Patients assigned treatment with tis-T in model may not receive infusion – accounted for by decision tree with proportions of patients receiving infusion assigned from pooled trial data



ERG's comments:

- Model assumes ineligibility will become known halfway through manufacturing period and patients assigned comparator costs and QALYs. Ineligibility will become known later → patients should accrue almost all costs of lymphodepleting and bridging chemotherapy
- Patients who become ineligible because of adverse events have a poor prognosis. Clinical advice to ERG indicates these patients would receive palliative care → assignment of comparator costs and QALYs inappropriate
- Scenarios examining the above assumptions have minimal effect on ICERs

Source: Company submission p93-98 (figures 25 and 26, table 26). ERG report p69-70

Tis-T overall survival (1)

Company's extrapolation: mixture cure model

- With exception of Gompertz curve standard parametric and spline models had poor visual/statistical fit
- Mixture cure approach justified as:
  - Pooled trial results show a plateau after 32 months up until latest follow-up of 5 years – suggestive of curative effect
  - Used in TA 450 (blinatumomab) and York regenerative medicine report (Hettle, 2017)
- Mixture cure approach carried out by:
  - Estimating fraction of patients cured based on logistical regression
  - Survival of cured patients based on general population mortality
  - Survival of patients not cured based on standard parametric distributions
  - General population mortality adjusted for ALL is applied from the point this mortality rate exceed that generated by the mixture cure model
- Present scenario analyses where standard parametric curves are used and patients are assumed to be cured at a specified time point (2, 3, 4 or 5 years)

Source: Company submission page 106-109

Tis-T overall survival (2)

Company's extrapolation: mixture-cure model

Cure fraction [redacted]

- Exponential used in base case: best statistical fit and cure fraction closest to percentage of patients alive after 5 years of follow-up from pooled efficacy data ([redacted])

ERG:

- Predicted cure fraction exceeds pooled number of EFS events of [redacted] - suggests cured fraction includes patients who relapse → inconsistent with long-term cure
- Log-logistic (used in ERG base-case) and Gompertz most plausible. Log-normal and generalised gamma have similar statistical fit and can't be completely excluded

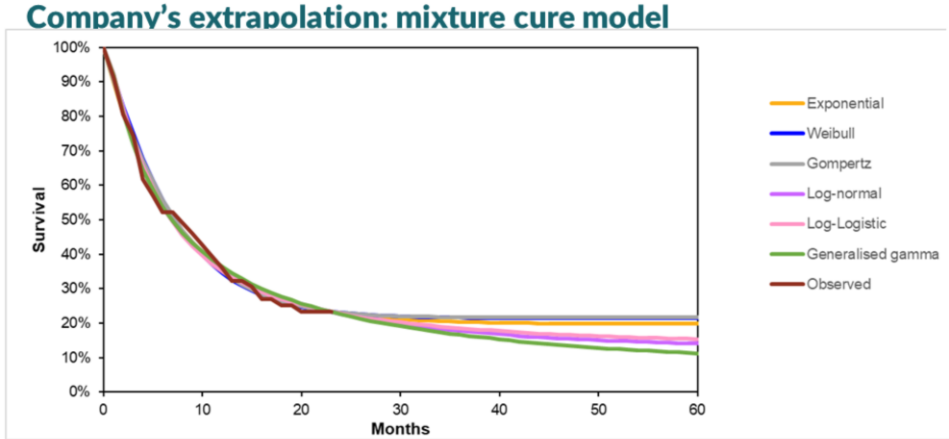
Source: company submission p109-110. figure 29 and table 30. ERG report p84

Notes:

ERG report states "uncertainty regarding the need to consolidate tisagenlecleucel-T response with SCT for patients to achieve long-term remission" as a further reason not to exclude lognormal and generalised gamma

Blinatumomab overall survival

Company's extrapolation: mixture cure model



	Cure fraction
Exponential	19.8%
Weibull	21.4%
Gompertz	21.7%
Log-normal	11.4%
Log-Logistic	12.1%
Generalised gamma	3.9%

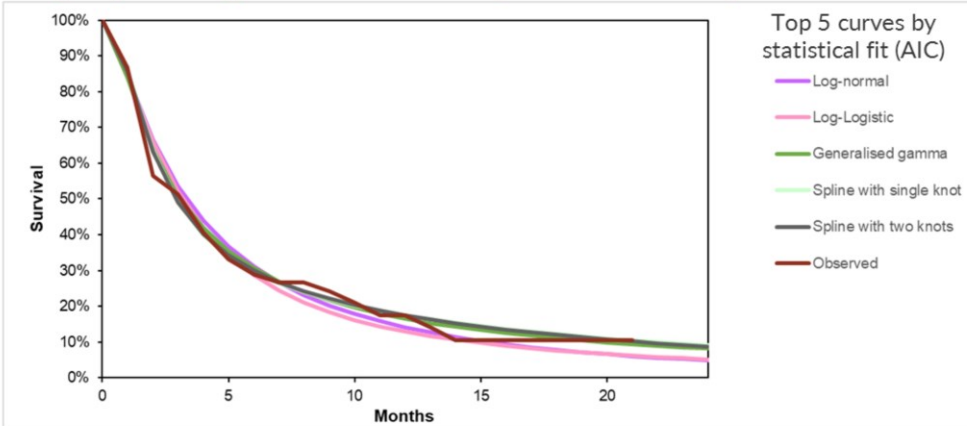
- Mixture-cure approach preferred as used in base-case for tis-T and bridging to allo-SCT with blinatumomab provides potential for cure
- Exponential, Weibull and Gompertz excluded – predicted implausibly high survival
- Log-normal used in base case as survival estimates judged to be plausible and statistical fit (AIC and BIC) superior to log-logistic

ERG: Agree with company that log-logistic and log-normal most plausible – prefer log-logistic as more closely matches Gompertz distribution from TA450 (blinatumomab)

Source: company submission p114-118. figure 29 and table 30, ERG report p86

Salvage chemotherapy overall survival

Company's extrapolation: standard parametric and spline models



- Clinician feedback suggested mixture-cure model inappropriate – predicted implausibly high survival
- Generalised gamma used in base case as predicted long term survival of approximately 3% of patients – considered clinically plausible

ERG: Prefer consistency of approach to modelling → explore use of mixture-cure model

Source: company submission p110-114. figure 31, ERG report p88

Summary of base-case OS extrapolations

Source: Figure 36 from company submission

45

Source: Company submission, figure 36, p119

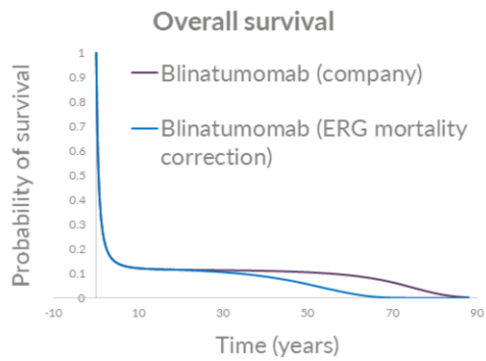
ERG's critique of overall survival extrapolations

- Underlying assumption of cure relies upon on the plausibility of tis-T inducing long-term curative remission – subject to considerable uncertainty given limited long-term data and tisagenlecleucel's novel mechanism of action
  - Exemplified by wide range of cure rates predicted by modelling (e.g [redacted] for tis-T)
- Company's scenario analysis of defining cure to occur at a particular time point and then applying an adjusted general population mortality rate is a plausible alternative and may be more appropriate given lack of long term data
- Despite uncertainties in the mixture-cure approach, ERG considers it appropriate for all comparators, justifications for using for FLA-IDA include:
  - Consistency of modelling approach between comparators
  - Clinical advice to the ERG suggests 10% of patients will be alive after 5 years, contrasting with the company's standard parametric base-case where only 3% of patients survive up to 3 years
  - Decrease in proportion of patients alive between 2 and 5 years with FLA-IDA is significantly higher than that for blinatumomab – clinically implausible as with both comparators, these patients will receive allo-SCT so proportions would be expected to be similar as they reflect effectiveness of allo-SCT

Source: ERG report p84-85, 88

ERG's correction to long term mortality

- ERG corrected an error regarding application of long term mortality in the mixture cure models:
  - modelled OS could not deviate from the curve estimated by the mixture cure model even when general population mortality based values were being used → ERG applied appropriate mortality rates. Change increases incremental cost effectiveness ratio from company base case by ~£3,500 vs salvage chemotherapy and ~£2,500 vs blinatumomab.
- Company states this approach was intended and that it reflects the most relevant survival estimates for the cured and uncured fractions in the mixture cure model
- Effect of change illustrated using blinatumomab survival curves

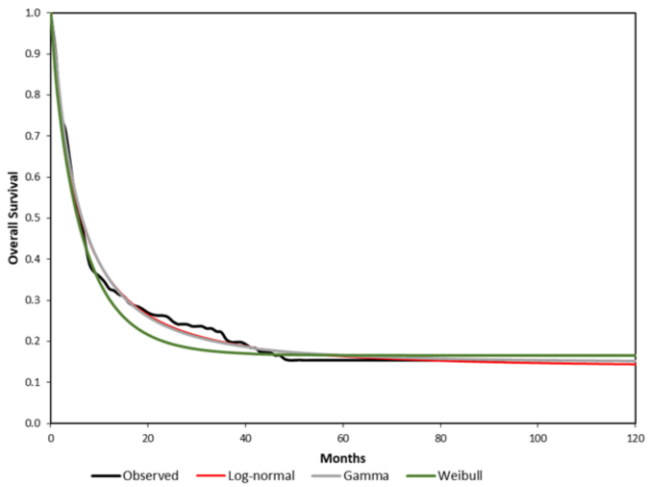


Source: ERG report, p120-121, table 19, company factual accuracy check response.

Figure not part of company submission or ERG report. Generated for illustrative purposes by NICE technical team from Markov trace in the company and ERG models ('Trace-Blinatumomab' sheet, column M).

ERG's alternative OS extrapolations for FLA-IDA

- ERG's preferred OS extrapolation for FLA-IDA based on data from Kuhlen 2017
  - Uses mixture-cure model – log-normal used in ERG base case
  - Scenarios applying mixture-cure model to clofarabine studies presented by company were also examined



Survival model	Cure fraction
Weibull	16.6%
Log-normal	13.7%
Generalised gamma	14.9%

Source: ERG report, p127-129, table 23

ERG's alternative assumptions for FLA-IDA

- In addition to OS extrapolation, ERG also applied the following assumptions relating to salvage chemotherapy
  - Event-free survival extrapolation based on mixture cure model (log-normal extrapolation, cure fraction 4.3%)
  - Adverse event rates from Jeha study may be overestimate as based on clofarabine → rates from FLAG-IDA arm of TOWER study of blinatumomab in adult ALL population applied
  - Proportion of patients receiving allo-SCT applied from Kuhlen (35%, compared with 16% in Jeha)

Survival model	Change from company base-case ICER vs salvage chemotherapy
Weibull	+£10,375
Log-normal	+£8,758
Generalised gamma	+£9626

Source: ERG report, p127-129, table 23

Notes: As discussed in clinical section ERG notes that differences in baseline characteristic between Kuhlen lead to an underestimate in overall survival for FLA-IDA and therefore favour tisagenlecleucel-T

Comparison of salvage chemotherapy survival curves

Proportion of patients alive (%)			
Company base case	[redacted]	[redacted]	[redacted]
ERG base case	24%	16%	14%

Figure not part of ERG report or company submission. Generated by NICE technical team from overall survival data in 'Efficacy' sheet of company and ERG models (truncated at 10 years).

Tis-T event-free survival (EFS)

Company's extrapolation: mixture cure model

- Standard parametric and spline models had poor visual/statistical fit
- Mixture cure generalised gamma used in base case: best statistical fit (along with Weibull and Gompertz), with cure rate consistent with overall survival model ([redacted])

ERG: Agrees that generalised gamma most plausible extrapolation, while noting that same uncertainties discussed for modelling of overall survival also apply to EFS

Source: company submission p122, figure 38 and table 40. ERG report p89-90

Comparator event-free survival (EFS)

Company's approach

- No EFS data were available for salvage chemotherapy and blinatumomab
- Hazard function for EFS assumed proportional to overall survival (OS)
  - Ratio modelled based on data from UK ALL study (patient population does not completely align with appraisal population)
  - Proportional relationship continues until year 5 with EFS assumed to be less than or equal to OS
  - After year 5 survival probabilities of EFS flatten until EFS=OS
- A scenario analyses using relapse-free survival data available from week 12 of the blinatumomab study was also conducted
  - EFS assumed to equal OS for first 12 weeks

ERG's comments:

- Approach taken by company appropriate
- ERG's base-case analysis uses data from Kuhlen 2017 for salvage chemotherapy EFS extrapolation

Source: company submission p122-123. ERG report p90. p127-128, 1p35-136.

Summary of event-free survival extrapolations

Company's base case

Source: Figure 39 from company submission

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Health-related quality of life

- Utility values from Kelly (2015) used in economic model
  - Used in Hettle (2017), obtained from large studies
  - ELIANA has limited EQ-5D data available, considered in scenario analysis

Parameter	Utility/disutility input	Source / Assumptions
Health state utility values (base case)		
Event-free survival (EFS)	0.91 (SD 0.16)	Kelly et al. (2015)
Progressive disease (PD)	0.75 (SD 0.02)	
Long-term survival	0.91 (SD 0.16)	
Health state utility values (scenario analysis)		
EFS	[redacted] (SD [redacted])	ELIANA (31st Dec 2017)
PD	[redacted] (SD [redacted])	

ERG's comments: 0.91 value from Kelly conditional on >5 years survival → considered scenario using EFS and PD values from ELIANA and long-term survival value from Kelly 2015 at either 2 years (incremental cost-effectiveness ratios [ICERs] vs comparators ↑ by £500) or 5 years (ICERs ↑ £1000)

Source: company submission p128-129, table 43. ERG report p92-93, p134

Disutility values for adverse events (AEs)

- Incidence of adverse events determined by pooled incidence from ELIANA, ENSIGN and B2101J
- AE rates for comparators from von Stackelberg and Jeha studies
- Treatment disutility values estimated from Sung et al.
  - Utility decrement of -0.42 applied for all therapies for duration of hospital stay (based on clinician feedback)
  - Utility decrement of -0.57 for 1 year applied for patients receiving allo-SCT (consistent with York regenerative medicines report, Hettle 2017)
- Utility decrement of -0.91 applied for patients experiencing Grade 3/4 cytokine release syndrome (CRS) for duration of ICU stay
  - For tisagenlecleucel the same decrement applied to non CRS-related ICU stays

ERG's comments: Jeha study likely to overestimate incidence of AEs for FLA-IDA chemotherapy as based on data for clofarabine, which has high toxicity → ERG exploratory analyses used AE incidence rates based on TOWER trial of blinatumomab in the adult ALL population and included FLAG-IDA as a comparator

55

Source: Company submission p124-125, p127-128. ERG report p90-94

ERG preferred a Lower disutility applied from 3 – 12 months post-SCT from Felder-Puig *et al*. Scenario analysis showed this change had minimal effect on the company's base case ICERs.

Costs – pre-treatment costs for tis-T

Tis-T	Cost*	Source/assumptions
Leukopheresis	£1,020.08	All patients in tisagenlecleucel-T arm incur this cost
Bridging chemotherapy	Drug costs: £85.10	Average dose per administration based on average body surface area data from ELIANA and ENSIGN Costs from eMIT 2017
	Administration costs: £986.07	Administration in outpatient setting for [redacted] based on clinician feedback and tis-T manufacturing time [redacted] of patents receive bridging chemotherapy based on pooled data from ELIANA and ENSIGN
Lymphodepleting chemotherapy	Drug costs: £122.46	Average dose per administration based on average body surface area data from ELIANA and ENSIGN Costs from eMIT 2017
	Outpatient administration costs: £269.04	[redacted] of patents receiving lymphodepleting chemotherapy based on data from ELIANA
	Hospital administration costs £7,101.38	[redacted] of patents receiving lymphodepleting chemotherapy, with average length of hospital stay of [redacted] days based on data from ELIANA

*Costs based on NHS reference costs 2016-2017 unless otherwise stated

eMIT, electronic market information tool; tisT, tisagenlecleucel T

Source: Company submission p131-137 (tables 44-46)

Costs – infusion costs for tis-T

Tis-T	Cost	Source/assumptions
Drug acquisition	£282,000	Includes shipping, manufacture and delivery
Drug administration	£19,959.03	All infusions take place in inpatient setting Average length of hospitalisation [redacted] days based on data from ELIANA Cost based on NHS reference costs 2016-2017
Cost of ICU stay (not due to CRS)	£2776.22	Average number of days in ICU for reasons other than CRS was [redacted] based on data from ELIANA Cost based on NHS reference costs 2016-2017
Total infusion costs	£304,735.26	

- Company: clinical expert feedback stated unlikely to treat patients in ICU for reasons other than CRS → cost of ICU stay conservative estimate

ERG's comments:

- Costs of treatment and pre-treatment generally appropriate
- Costs associated with training of medical staff not quantified

CRS, cytokine release syndrome

57

Source: Company submission p138-139 (table 47). ERG report, p97-98

Costs – adverse event costs for tis-T (1)

Tis-T	Cost	Source/assumptions
Cytokine release syndrome (CRS)	£18,029.18	Average number of days in ICU for CRS was [redacted] and average number of doses of tocilizumab [redacted] based on data from ELIANA Cost of ICU stay based on NHS reference costs 2016-2017 Cost of tocilizumab based on BNF 2018

- Company: number of days in ICU may be overestimated as a result of less frequent use of tocilizumab to treat CRS in early stages of trial → cost of ICU stay conservative estimate

ERG's comments: ICU may be required to hold "spare bed" in anticipation of CRS event → cost included in ERG base-case (ICERs ↑ by approx. £1,000-£1,500)

58

Source: Company submission p138-139 (table 47). ERG report p104-106, p133.

Costs – adverse event costs for Tis-T (1)

Tis-T	Cost	Source/assumptions
B-cell aplasia	£11,284.82	All patients with B-Cell aplasia (73%) require intravenous immunoglobulin (IVIG) treatment for duration of their aplasia Average treatment duration 11.40 months based on data from ELIANA IVIG cost based on BNF 2018

ERG's comments:

- Clinical advice to ERG suggests only patients with frequent infections and low immunoglobulin levels require IVIG treatment → company may have overestimated proportion of patients receiving IVIG
- Analysis based on proportion of patients with hypogammaglobulinaemia in ELIANA ([redacted]) used in ERG base-case ↓ ICER by approx. £1,000-£1,500)
- [redacted] of patients yet to achieve B-cell recovery after 2 years therefore treatment duration likely to be underestimated→ explore alternative treatment duration in scenario analyses

IVIG duration	3 years	5 years	[redacted] of patients in EFS state on IVIG treatment
Increase in ICER	£515-£708	£1,651-£2,269	£6,296-£8,654

BNF, British National Formulary

Source: Company submission p138-139 (table 47). ERG report, p104-106, p129-130, p133

Costs – subsequent treatment

Tis-T	Cost	Source/assumptions
Stem cell transplant (SCT)	£116,311.44	Cost based on NHS reference costs 2016-2017 (for cost of harvesting stem cells and transplant procedure) and UK Stem Cell Strategy Oversight Committee (for cost of follow up)

- Rates of subsequent allo-SCT:

Intervention	Rate of subsequent allo-SCT	Source
Tisagenlecleucel	[redacted]	Pooled tisagenlecleucel clinical trials
Salvage chemotherapy – company	16.39%	Jeha
Salvage chemotherapy – ERG	35.26%	Kuhlen
Blinatumomab	34.29%	Von Stackelberg

60

Costs – blinatumomab

- ERG: Clinical advice to ERG suggests that patients would be unlikely to receive more than 2 cycles of blinatumomab before progressing to stem cell transplant (marketing authorisation allows maximum of 5 cycles)
- ERG's base case includes assumption that patients could receive no more than 2 cycles of blinatumomab
- Increases incremental cost-effectiveness ratio (ICER) of tis-T compared with blinatumomab by £2,050

61

Source: Erg report p132, p135

Notes:

NICE TA 450 (blinatumomab) section 4.16 states that "If the disease responded after 2 cycles but a suitable donor match was not immediately available, or if stem cell transplantation was not appropriate, they might have more than 2 cycles."

Summary of company's base case model

	Assumptions and adjustments
Clinical comparison	• Clofarabine used as proxy for efficacy of FLA-IDA salvage chemotherapy

Extrapolation	• Mixture cure model for tis-T
	  • OS – exponential ([redacted] cure fraction)
	  • EFS – generalised gamma ([redacted] cure fraction)
	• Mixture cure model for blinatumomab
	  • OS – log-normal (11.4% cure fraction)
	  • EFS – based on OS
	• Standard parametric distribution for salvage chemotherapy
	  • OS – generalised gamma, EFS based on OS

HRQoL	• Utility values from Kelly 2015
Costs	• Training costs not quantified • Patients can receive more than 2 cycles of blinatumomab • No requirement to hold spare ICU bed for CRS • All patients with B-cell aplasia are treated with IVIG for 11.4 months

AEs, adverse events; CRS, cytokine release syndrome; EFS, event-free survival; HRQoL, health related quality of life; OS; overall survival; tis-T, tisagenlecleucel-T

Source: Company submission, p154-155 table 59

Company's Results – deterministic base-case

	Total			Incremental			
Technologies	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)
List price							
Tis-T	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With patient access scheme for tisagenlecleucel-T							
Tis-T	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392

ICER, incremental cost effectiveness ratio; LYG, life years gained; Tis-T, tisagenlecleucel-T; QALY, quality-adjusted life year.

Source: Company submission p157-158, table 61 and 62

ERG's correction to company's model

- ERG corrected an error regarding application of long term mortality in the mixture cure models:

	Total		Incremental			
Technologies	Costs	QALYs	Costs	QALYs	ICER	Δ ICER
Company's base-case results						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£25,404	-
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£18,392	-
Company's base-case results including ERG's mortality calculation correction						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,806	+£3,402
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£20,864	+£2,471

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life year

Source: ERG report, p120-121, table 19, company factual accuracy check response

Company's results – probabilistic

	Total		Incremental		
Technologies	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
List price					
Tis-T	[redacted]	[redacted]			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With patient access scheme for tis-T					
Tis-T	[redacted]	[redacted]			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£27,066
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£20,046

ICER, incremental cost effectiveness ratio; LYG, life years gained; tis-T, tisagenlecleucel-T; QALY, quality-adjusted life year.

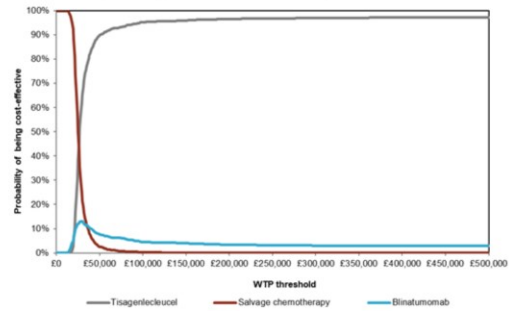
Source: Company submission p163, table 64 and 6

Company's probabilistic sensitivity analysis

Cost effectiveness plane: tis-T (PAS price) vs salvage chemotherapy

[redacted]

Cost effectiveness acceptability curve: tis-T (PAS price) vs all comparators



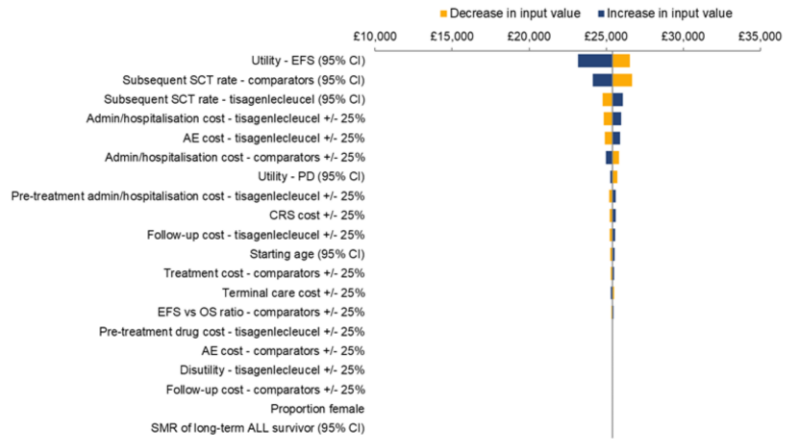
- Company: When considering tis-T at PAS price the probability of tisagenlecleucel being the most cost-effective treatment option is 90% at the £50,000 per QALY gained threshold and 65% at the £30,000 per QALY gained threshold

PAS, patient access scheme, tis-T, tisagnelecleucel-T, QALY, quality adjusted life year

Source: company submission p163-166 (figures 42 and 45)

Company's one way sensitivity analysis

Deterministic sensitivity analysis: tis-T (PAS price) vs salvage chemotherapy



- Company: Results most sensitive to subsequent allo-SCT rate and utility values applied for event-free survival

AE, adverse event; CI, confidence interval; CRS, cytokine release syndrome; EFS, event-free survival; OS, overall survival; PAS, patient access scheme; PD, progressed disease; SCT, stem cell transplant; SMR, standardised mortality ratio.

Key company scenario analyses

- All incremental cost-effectiveness ratios (ICERs) based on patient access scheme price for tisagenlecleucel-T

Scenario	Range of ICERs	
	Versus blinatumomab	Versus salvage chemotherapy
Base case	£18,392	£25,404
Alternative mixture cure overall survival extrapolations for tisagenlecleucel-T	£19,051-£21,762	£25,368-£28,641
Alternative overall survival extrapolation using standardised mortality ratios (applied after 5 years)	£20,030-£22,093	£28,942-£33,799
Alternative data sources for clofarabine efficacy using using parametric curves (Kantarjian 2017, von Stackelberg 2011, Hijiya 2011, Locatelli 2009)	Minimal effect	£20,890-£27,615
Alternative data sources for clofarabine efficacy using using mixture cure model (Hijiya 2011, Locatelli 2009)	Minimal effect	£28,590-£38,883
Utility values from ELIANA trial in place of values from literature (Kelly)	£20,907	£28,937

Source: Company submission, p171-176, tables 67-73

Notes: Alternative time points for application of standardised mortality ratios were also examined.

Discount rate

Treatment	Discount	Incremental costs	Incremental QALYs	Company's ICER	% change from base-case ICER
Salvage chemotherapy	1.5%	[redacted]	[redacted]	£16,202	-36%
Blinatumomab	1.5%	[redacted]	[redacted]	£11,747	-36%

NICE methods guide	Company
• Reference case should use a discount rate of 3.5% for both costs and benefits • Differential discounting should be applied where treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years)	• Costs and benefits discounted at 3.5% annually in base case • Provide scenario analyses of discount rates of 1.5% and 5%

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

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Source: company submission table 71, page 175

Scenario analyses with discount rate of 1.5% are available in ERG addendum and the associated confidential appendix

Summary of ERG's base case model

	Assumptions and adjustments
Clinical comparison	• **Salvage chemotherapy data from Kuhlen 2017** (use of mixture cure model, reduced incidence of AEs and increased subsequent allo-SCT) –ICER vs salvage chemotherapy ↑ by £7,706

Extrapolation	• Mixture cure model for tisagenlecleucel-T
	  • **OS – log-logistic** ([redacted] cure fraction) – ICER vs both comparators ↑ by approx. £2,800
	  • EFS – generalised gamma ([redacted] cure fraction)
	• Mixture cure model for blinatumomab
	  • **OS – log-logistic** (12.1% cure fraction)
	  • EFS – based on OS
	• **Mixture cure model for salvage chemotherapy**
	  • OS and EFS both log-normal (cure fractions 13.7% and 4.3%)

HRQoL	• **Utility values up to 2 years from ELIANA, long term survivors from Kelly** – ICER vs both comparators ↑ by £404
Costs	• **Patients receive only 2 cycles of blinatumomab** – ICER vs blinatumomab ↑ by £1,803 • **Included costs of holding spare ICU bed for CRS** – ICER vs blinatumomab ↑ by £1342, vs salvage chemo ↑ by £978 • **Patients with hypogammaglobulinaemia** treated with IVIG for 11.4 months – ICER vs blinatumomab ↓ by £1,436, vs salvage chemo ↓ by £1,046

AEs, adverse events; CRS, cytokine release syndrome; EFS, event-free survival; HRQoL, health related quality of life; OS; overall survival, SCT, stem cell transplant. Changes for company base case highlighted in **bold**.

Source: ERG report p134-137, table 29

Results – ERG's base case

Technologies	Total		Incremental			
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	Δ ICER from CBC
Deterministic (with tis-T patient access scheme price)						
Tis-T	[redacted]	[redacted]	-			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£45,397	£19,992
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£27,732	£9,339
Probabilistic (with tis-T patient access scheme price)						
Tis-T	[redacted]	[redacted]	-			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£48,265	£22,861
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£29,501	£11,109

CBC, company base case; ICER, incremental cost effectiveness ratio; LYG, life years gained; Tis-T, tisagenlecleucel-T; QALY, quality-adjusted life year.

Source: ERG report p136, table 29

Exploratory analyses on ERG's base case

- All incremental cost-effectiveness ratios (ICERs) based on patient access scheme price for tis-T and are probabilistic analyses

Scenario	Range of ICERs	
	Versus blinatumomab	Versus salvage chemotherapy
ERG's base case (probabilistic)	£29.501	£48,265
Rates of SCT after treatment with tis-T from 0% (tis-T curative) to 100% (tis-T used as bridge to SCT)	£23,900-£46,133	£41,274-£65,229
B-cell aplasia and hypogammaglobulinaemia persist for 3 years or indefinitely (compared with 11.4 months in ERG's base case)	£30,695-£40,192	£48,475-£58,342
OS base on lognormal cure model – worst case scenario where benefits do not persist over long term (predicts cure fraction of ([redacted] compared with ([redacted] in ERG's base case)	£44,299	£74,322

OS, overall survival; SCT, stem cell transplant; tis-T, tisagenlecleucel-T

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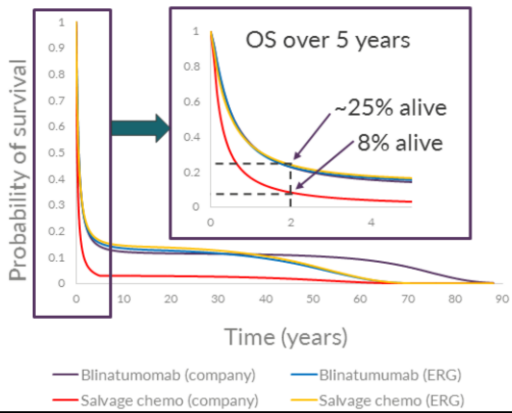
ERG report p137-139, table 30.

Notes:

ERG consider rate of SCT after tis-T being 0% to be a plausible scenario in clinical practice. Use as bridge to SCT is not intended use of tis-T but is in line with use of other CAR-T therapies as bridge to SCT.

End of life – Life expectancy

Criterion	Company submission	ERG's comments
Life expectancy less than 24 months	Criterion met • von Stackelberg et al. (2016) – median OS with blinatumomab = 7.5 months. • Jeha et al, (2006) – median OS with clofarabine (proxy for savage chemotherapy) = 13 weeks • Criterion met in previous appraisals of blinatumomab and inotuzumab	Base case results for mean OS (undiscounted) Blinatumomab: Company – [redacted] years ERG – [redacted] years Salvage chemotherapy: Company – [redacted] years ERG – [redacted] years Uncertain whether criterion met



- Difference in estimates for salvage chemotherapy driven by use of alternative data source and mixture cure model by ERG
- Mean overall survival estimates from model driven by long-term survivors
  - Blinatumomab cure fraction: 11% in company model, 12% in ERG model
  - Salvage chemo cure fraction: 14% in ERG's model

Source: Company submission table 24, p87-88, ERG report p141

Figure not part of company submission or ERG report. Generated by NICE technical team for illustrative purposes from Markov trace in the company and ERG models ('Trace-Blinatumomab' and 'Trace-Chemo' sheets, column M).

End of life – Life extension

Criterion	Company submission	ERG comments
Extension to life greater than 3 months	Criterion met Median OS from the latest data cuts of the three tisagenlecleucel clinical trials: • ELIANA: [redacted] with a max OS follow-up of [redacted] months • ENSIGN: 23.8 months (95% CI: 8.8 to NE) with a max OS follow-up of [redacted] months • B2101J: [redacted] months [redacted] with a max OS follow-up of [redacted] months	Base case results for mean life extension (undiscounted) Blinatumomab: Company – [redacted] years ERG – [redacted] years Salvage chemotherapy: Company – [redacted] years ERG – [redacted] years Probable but uncertain that criterion met (uncertainty due to significant differences between tis-T and comparator studies)

CI, confidence interval; NE, not estimable; OS, overall survival

Source: Company submission table 24, p87-88, ERG report p141

Equality

- No equality factors identified in company submission
- During scoping it was noted that "Blood support or haematopoietic stem cell transplantation are not acceptable to some religious groups such as Jehovah's witnesses these patients would receive best supportive care"
- *Population includes children: any additional considerations required?*

Innovation

- **Company considers tis-T to be innovative:**
  - "Represents a paradigm shift" in the management of paediatric and young adult relapsed/refractory ALL
  - Only a single infusion required
  - Potentially curative approach for patients with an otherwise poor prognosis
  - Substantial positive impact on patient and caregiver (for example, allowing return to school/university/employment) has not been captured within the economic analysis
- **Clinical expert statements:**
  - The technology is innovative and can cure new subsets of patients
  - The technology is a 'step-change' in the management of ALL

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 22 August 2018

Deadline for comments **12pm Monday 13 August 2018** email: **tacommc@nice.org.uk /NICE DOCS**

About you

Your name	[redacted]
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals Ltd
Are you (please tick all that apply)	☒ a representative from the company (Novartis)? ☐ a clinical expert? ☐ a commissioning expert? ☐ a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Questions for engagement

Question 1: What population are likely to receive tisagenlecleucel-T for relapsed or refractory B-cell ALL in clinical practice?	
Is tisagenlecleucel likely to be used for people with Philadelphia positive disease?	Patients with Philadelphia chromosome-positive ALL were eligible for inclusion in the tisagenlecleucel trials if they had failed or were intolerant to two lines of tyrosine kinase inhibitor (TKI) therapy, or were contraindicated for TKI therapy. These patients are also included within the anticipated licence for tisagenlecleucel (the licence does not stipulate either Philadelphia chromosome-positive or Philadelphia chromosome-negative disease). There is no reason to suggest that tisagenlecleucel should not be used in these patients in UK clinical practice. It should be noted that the number of patients with Philadelphia chromosome-positive ALL in this setting that would be eligible for tisagenlecleucel is extremely small, and is anticipated to be only

	one or two patients per year in England. For these patients, treatment options are severely limited, and prognosis is extremely poor. The inclusion of these patients within the tisagenlecleucel trials and within the tisagenlecleucel licence therefore offers these patients a possible treatment option and the hope for a cure.
Are the results for Philadelphia negative disease generalisable to those with Philadelphia positive disease?	Results from the ELIANA, ENSIGN and B2101J clinical trials do not report outcomes for Philadelphia chromosome-positive (*BCR-ABL1*) ALL patients specifically, as the number of patients with this specific disease type were so small (analyses were only to be performed if at least five patients were present in each subgroup). However, subgroup analyses were conducted for overall remission rate (ORR) in ELIANA and ENSIGN for patients with a range of genetic abnormalities, including those with Philadelphia chromosome-positive ALL, as well as those with *MLL* rearrangement, hypodiploidy, *BCR-ABL1*-like gene signatures and complex karyotypes (≥5 unrelated abnormalities). The results of these analyses were consistent with those of the full analysis set (FAS) in both ELIANA and ENSIGN, with high response rates (ORR was [redacted] in both trials for patients with genetic abnormalities), demonstrating that the efficacy associated with tisagenlecleucel is consistent irrespective of the presence of genetic abnormalities such as the Philadelphia chromosome; therefore, the results achieved in the tisagenlecleucel clinical trials overall can be considered generalisable to patients with Philadelphia chromosome-positive disease.
Question 2: What is the treatment pathway for people younger than 18 years of age with primary refractory B-cell ALL?	
Do people younger than 18 years of age with primary refractory B-cell ALL routinely receive treatment based on the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol?	No. Based on UK clinical expert feedback, patients under the age of 18 years with primary refractory B-cell ALL *do not* routinely receive treatment based on the NOPHO protocol. As there are so few patients with primary refractory ALL, and a lack of clinical guidelines in the UK for these patients specifically, choice of treatments vary between individual patients and treatment centres and there is not one universally-used protocol. The clinical experts consulted at the time of writing the company submission did not mention the NOPHO protocol for primary refractory patients. Their feedback was that FLA-IDA and blinatumomab are primarily used as potential treatment options for these patients in current clinical practice. Therefore, it is not the case that patients with primary refractory ALL routinely

	receive treatment based on the NOPHO protocol in England, and instead several treatment options may be tried in this setting.
Is the company's position of tisagenlecleucel-T in the treatment pathway for people younger than 18 years of age with primary refractory disease appropriate?	Primary refractory patients were eligible for inclusion within the ELIANA, ENSIGN and B2101J clinical trials if they had primary refractory ALL as defined by not achieving a complete remission (CR) after two cycles of a standard chemotherapy regimen. These patients are also included within the anticipated licence for tisagenlecleucel. Therefore, there is no reason to suggest that these patients would not be eligible for tisagenlecleucel in UK clinical practice at this point in the treatment pathway. In addition, the fact that there are existing, effective treatments for patients with primary refractory disease does not preclude the use of tisagenlecleucel in primary refractory patients, nor the ability for tisagenlecleucel, as a novel agent, to displace current practice.
Question 3: What is the current treatment pathway for people with B-cell ALL with 2 or more disease relapses?	
Where is blinatumomab used in the current treatment pathway for Philadelphia negative disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	**Patients <18 years:** feedback from UK clinical experts at the time of writing the company submission was that the vast majority of patients <18 years of age with B-cell ALL receive treatment according to the ALLR3 protocol following a first relapse, and blinatumomab is most commonly reserved for use following two or more relapses. In recent weeks however, paediatricians at Great Ormond Street Hospital have started to use blinatumomab as an option to treat high risk patients in first relapse (although it is our understanding that many other centres still treat according to the ALLR3 protocol). When used following a first relapse, the feedback from clinical experts at Great Ormond Street Hospital was that blinatumomab would typically be given for one cycle or occasionally two cycles (compared with the 5 of 6 cycles that would be required following 2 or more relapses). As only 1 or 2 cycles of blinatumomab would be given in this setting, the possibility of CD-19 escape is negligible and therefore the use of blinatumomab at this stage would not preclude the use of further blinatumomab or indeed the use of tisagenlecleucel following a second relapse. **Patients >18 years:** In some centres blinatumomab may be offered earlier on in the treatment pathway, following a first relapse. In other centres, patients are treated with blinatumomab following two or more disease relapses.

Is blinatumomab an appropriate comparator to tisagenlecleucel-T for relapsed disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	Blinatumomab is an appropriate comparator for patients both <18 years and >18 years as it is a treatment option offered to patients at an equivalent point in the treatment pathway to where tisagenlecleucel is anticipated to be placed. This is supported by feedback from UK clinical experts who confirmed that blinatumomab, along with salvage chemotherapy (FLA-IDA), were the current standards of care for paediatric and young adult patients with a second or later relapse of ALL in both age groups. Although blinatumomab may be offered to some patients following a first relapse, this does not preclude its use at a later treatment line. Therefore, blinatumomab remains a comparator to tisagenlecleucel at second or later relapse. Furthermore, feedback from UK clinical experts was that the use of one or two cycles of blinatumomab following a first relapse would be highly unlikely to result in a CD19-negative relapse, and therefore the use of blinatumomab at this stage would not preclude the use of tisagenlecleucel following a second relapse.
Question 4: Is it appropriate to use clofarabine as a proxy for the efficacy of FLA-IDA (that is salvage chemotherapy)?	
Is clofarabine used in clinical practice in the NHS in England?	Feedback from UK clinical experts is that clofarabine is used very rarely in UK clinical practice. Although it has been approved by the EMA for the treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response, the consensus from UK clinical experts was that the toxicity profile of clofarabine was inappropriate for use in the majority of patients. Therefore, clinicians choose to use FLA-IDA, which they consider to be as effective as clofarabine but associated with less toxicity.
Is there any evidence to support the equivalence of FLA-IDA and clofarabine?	In the absence of any relevant trials evaluating FLA-IDA, Novartis sought expert clinical feedback in order to produce a comparison versus salvage chemotherapy within the company submission. Four UK clinical experts were consulted as part of this appraisal and all four agreed that the efficacy of clofarabine monotherapy observed in the Jeha *et al.* (2006) trial were consistent with outcomes observed in clinical practice and could be considered reflective of FLA-IDA. In addition, Jeha *et al.* (2006) was selected as the efficacy source for standard of care chemotherapy in the mock appraisal of CAR-T therapies conducted by the University of York. Novartis fully acknowledge that the use of Jeha *et al.* (2006) as a proxy for the efficacy of FLA-IDA is associated with uncertainty and therefore conducted several scenario analyses evaluating different sources of data for the efficacy of FLA-IDA within the company submission, namely; von

	Stackelberg *et al.* 2011, Kantarjian *et al.* 2017 (both of which investigated a mixture of chemotherapy regimens) and Hijiya *et al.* 2011 (clofarabine, etoposide and cyclophosphamide). These scenarios were not associated with significant changes to the base case results of the economic model, with ICERs (with PAS) for tisagenlecleucel versus salvage chemotherapy of £20,890, £26,743 and £27,615, respectively, compared to the base case ICER of £25,404. Therefore, Novartis believe we have made every effort to produce as robust a comparison versus salvage chemotherapy as was possible, and have accompanied this with several scenarios to explore any potential uncertainty. Based on these results, the ICERs versus salvage chemotherapy when using the various sources of efficacy data consistently remained below a cost-effectiveness threshold of £30,000 per QALY gained. Finally, it is important to note that the ERG's preferred source of efficacy data for salvage chemotherapy (Kuhlen *et al.* 2017) is associated with several limitations: • The proportion of patients with a previous allo-SCT was 100% in Kuhlen versus 54.2% in the tisagenlecleucel trials, hence it has only been conducted in a subset of the population potentially eligible for tisagenlecleucel and the Jeha 2006 study is therefore more inclusive of the overall population. However, 26.3% of patients received a further subsequent SCT. Second SCTs are extremely rare in the UK in this patient population, which raises questions about the representativeness of this study to UK practice. The high rate of SCT is biasing results against tisagenlecleucel as SCT is a curative option and therefore OS in this study is a clear overestimate. • Patients with extramedullary relapse (which are shown to have statistically significantly better outcomes for both OS and EFS) were excluded from the tisagenlecleucel trials, but represent 19.7% of the patient population in the Kuhlen et al. paper. • Finally, the HR for OS and EFS for T-ALL versus B-ALL (Table II in the Kuhlen study) was also not statistically significant and therefore it is misleading to state that there is a difference in outcomes between these groups. It is important to acknowledge when differences are not significant as this prevents misinterpretations of data. Non-significant data may result from chance rather than an actual observed difference. Taken together, Novartis believe these limitations discredit the Kuhlen study from being a more appropriate source of efficacy data than the Jeha 2006 study used within the company submission.

Question 5: Long term usage and costs of IVIG treatment - real world experience	
Would people younger than 18 years of age require continued IVIG treatment and for how long?	Consensus from several UK clinical experts consulted in response to this question was that a lifetime duration of IVIG is clinically implausible and the duration of IVIG treatment in patients <18 years of age would be aligned with the duration of B-cell aplasia; the estimate of 11.4 months used in the base case of our submission (which was based on the time to B-cell recovery), was therefore validated by UK clinical experts and is considered appropriate. Clinical experts also stated that when paediatric patients transition to the adult population (i.e. >18 years of age), they would be treated according to the adult protocol (see below). This involves the receipt of IVIG only if a patient has B-cell aplasia alongside a severe infection or severe cytomegalovirus (CMV) reactivation. This only occurs in approximately 20% adult patients, and patients would be treated with IVIG for 6-12 months only.
Would people aged 18-25 years require continued IVIG treatment and for how long?	As highlighted above, patients with r/r B-cell ALL aged 18–25 would not receive continued IVIG treatment following infusion with tisagenlecleucel. Feedback from UK clinical experts sought in response to this question was that patients will only receive treatment with IVIG if they have B-cell aplasia alongside a severe infection or severe CMV reactivation. This only occurs in approximately 20% adult patients, and patients would be treated with IVIG for 6-12 months only. It should be noted that this feedback was received after the company submission to NICE, and therefore the assumptions made within the company base case with regards to the administration of IVIG were conservative.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed response form

Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK

Appendix

Re: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) in people aged up to 25 years [ID1167] – updated data cut-off from the ELIANA clinical trial

Latest data cut-off from the ELIANA clinical trial (13th Apr 2018)

The latest data cut-off from ELIANA (13th Apr 2018) is the second presented to the Committee, following the initial data cut-off (31st Dec 2017), which were presented in the initial company submission. A summary of the latest data cut-off (13th Apr 2018) compared to that presented in the company submission (31st Dec 2017) is presented below in Table 1. As is evident in Table 1, the results from the updated data cut-off (13th Apr 2018) are consistent with those from the data cut-off presented within the company submission (31st Dec 2017). These data highlight the robustness of the data presented initially, and continue to support the clinical benefits of tisagenlecleucel in paediatric and young adult patients with ALL and the assumptions upon which the economic analysis within the company submission were based.

All data from the 31st Dec 2017 and 13th Apr 2018 data cut-offs for the ELIANA clinical trial are academic in confidence and should remain confidential.

Table 1: Overview of clinical effectiveness results from the ELIANA clinical trial

n (%)	ELIANA 31st Dec 2017 (N=79) (N=77 for ORR and DoR)[a]	ELIANA 13th Apr 2018 (N=79)
Primary efficacy results		
BOR[b]		
ORR (CR+CRi) (95% CI; p value)	[redacted]	[redacted]
CR	[redacted]	[redacted]
CRi	[redacted]	[redacted]
NR/Unknown[d]	[redacted]	[redacted]
ORR with bone marrow MRD negative (i.e. MRD <0.01%) (95% CI; p value)	[redacted]	[redacted]
Secondary efficacy results		
DoR (/RFS)		
% event free at 6 months (95% CI)	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]
EFS		

% event free at 6 months (95% CI)	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]
OS		
% at 6 months (95% CI)	[redacted]	[redacted]
% at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]

[a]ORR and DoR from the 31st Dec 2017 data cut-off for the ELIANA clinical trial were assessed in patients at least 3 months post-tisagenlecleucel infusion only (efficacy analysis set). [b]BOR is reported within 3 months for the ELIANA clinical trial. [c]No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented. [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.

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: CR with incomplete blood count recovery; DoR: duration of remission; MRD: minimum residual disease; NE: not estimable; NR: non-responder/no remission; ORR: overall remission rate

Source: ELIANA CSR (31st Dec 2017);[1] ELIANA CSR (13th Apr 2018).[2]

Event-free survival

At the latest data cut-off (13th Apr 2018), in the full analysis set (FAS), [redacted] of the [redacted] patients (39.2%) per IRC review reported treatment failure, relapse or death due to any cause after remission prior to the data cut-off. The median EFS was [redacted]. The estimated event-free probability was [redacted] (95% CI: [redacted]) at Month 6 and [redacted] (95% CI: [redacted]) at Month 12 and Month 18. The Kaplan-Meier plot for EFS per IRC assessment is presented in Figure 1.

Figure 1. Kaplan-Meier Plot for EFS censoring allo-SCT by IRC assessment in the ELIANA clinical trial (13th Apr 2018; FAS)

[redacted]

Abbreviations: allo-SCT: allogeneic stem cell transplantation; CI: confidence interval; EFS: event-free survival; FAS: full analysis set; IRC: Independent Review Committee; NE: not estimable.

Source: ELIANA CSR (13th Apr 2018).[2]

Overall survival

At the latest data cut-off (13th Apr 2018), in the FAS, [redacted] patients ([redacted]) died after tisagenlecleucel infusion and the estimated probability of survival was [redacted] (95% CI: [redacted]) at Month 6, [redacted] (95% CI: [redacted]) at Month 12 and [redacted] (95% CI: [redacted]) at Month 18. Median OS was [redacted]. The Kaplan-Meier plot for OS is presented in Figure 2.

Figure 2: Kaplan-Meier plot for OS in the ELIANA clinical trial (13th Apr 2018; FAS)

Abbreviations: CI: confidence interval; FAS: full analysis set; NE: not estimable; OS: overall survival.
Source: ELIANA CSR (13th Apr 2018).[2]

References

1. 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.
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 (13th April 2018 data cut-off). Data on File. 2018.

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Technical engagement response form

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 22 August 2018

Deadline for comments **12pm Monday 13 August 2018** email: **tacommc@nice.org.uk /NICE DOCS**

NICE National Institute for Health and Care Excellence

About you

Your name	**Prof Peter Clark**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England**
Are you (please tick all that apply)	☐ a representative from the company (Novartis)? ☐ a clinical expert? **x** a commissioning expert? ☐ a patient expert or organisation? **x** an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Questions for engagement

Question 1: What population are likely to receive tisagenlecleucel-T for relapsed or refractory B-cell ALL in clinical practice?	
Is tisagenlecleucel likely to be used for people with Philadelphia positive disease?	Yes. The Ph pos ALL population is very small in young patients with ALL and there is no biologically plausible reason as to why such patients would not be treated with T-L CAR T cell therapy. NHS England notes that such patients were included in the T-L trials.
Are the results for Philadelphia negative disease generalisable to those with Philadelphia positive disease?	See above

Question 2: What is the treatment pathway for people younger than 18 years of age with primary refractory B-cell ALL?	
Do people younger than 18 years of age with primary refractory B-cell ALL routinely receive treatment based on the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol?	Yes. The numbers of patients with disease refractory to 1st line therapy are small and were also small in the T-L trials. NHS England observes that the current standard treatment for disease refractory to 1st line induction in those aged 18 years or less is mainly using the NOPHO protocol. This was not recognised in the company's submission. For those aged over 18 years (a much smaller group), the current treatment is blinatumomab or combination chemotherapy and more likely to be blinatumomab. Thus there is some current blinatumomab use in this population although this will soon be displaced by inotuzumab.
Is the company's position of tisagenlecleucel-T in the treatment pathway for people younger than 18 years of age with primary refractory disease appropriate?	NHS England concludes that the comparator for 1st line refractory patients aged 18 yeasr or less should be mainly the NOPHO protocol as this is used in children and teenagers. Currently, there is also some blinatumomab use in young adults but such use of blinatumomab is likely to diminish in favour of inotuzumab.
Question 3: **What is the current treatment pathway for people with B-cell ALL with 2 or more disease relapses?**	
Where is blinatumomab used in the current treatment pathway for Philadelphia negative disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	For patients who respond to 1st line induction and then relapse, the aim of treatment is attain a second remission and then consolidate this with an allogeneic SCT. For patients who relapse post-SCT, the company has stated that the standard comparators are either combination cytotoxic chemotherapy FLA(G)-IDA or the CD19-targeted monoclonal antibody blinatumomab. The company states that FLA(G)-IDA and blinatumomab are also the comparators for patients in 2nd or further relapse. Blinatumomab is a specific T-cell engager antibody which binds specifically to CD19 expressed on the surface of cells of B-lineage and also to CD3 expressed on the surface of T cells. It thus activates T cells by connecting the CD3 on the T cell with CD19 on benign and malignant B cells. Blinatumomab is recommended by NICE as a treatment

	option in adults with relapsed/refractory Philadelphia chromosome negative ALL. Blinatumomab access has been extended to the non-adult ALL population by NHS England. The administration of blinatumomab is inconvenient and demanding for patients and clinical staff. Of note too is that approximately 22% of patients who relapse post blinatumomab do so with ALL which no longer expresses CD19. T-L CAR T cell therapy also targets CD19 and as a consequence there is therefore a concern that patients previously treated with blinatumomab and who then relapse may have clones of B cells which do not express CD19. In such circumstances, treatment with T-L would therefore not be expected to have any significant chance of curing the patient. The 3 T-L trials excluded patients previously treated with blinatumomab and thus there is no evidence of the efficacy of T-L in patients previously treated with blinatumomab. As a consequence of the biological plausibility of prior blinatumomab reducing the benefits of CAR T cell treatment directed at CD19 plus the exclusion of patients with prior blinatumomab exposure in the T-L trials, there will be wariness by haematologists in the use of blinatumomab if CAR T cell therapy with T-L is a potential salvage therapy later in the treatment pathway. Although combination chemotherapy and blinatumomab were commissioned options for relapsed/refractory ALL at the times of the NICE scope and the Novartis and ERG submissions, inotuzumab ozogamicin is now NICE-recommended in adults with relapsed/refractory ALL and funding has been extended to children by NHS England. Inotuzumab is directed against CD22 and thus does not carry any biological plausibility in potentially reducing the benefits of subsequent T-L therapy. In addition, it is a much more convenient drug to receive and deliver than blinatumomab. Hence it is likely to rapidly displace much use of blinatumomab and especially so in the relapsed/refractory ALL population in which CAR T cell therapy with T-L could be an option later in the treatment pathway. The administration costs of inotuzumab are much less than for blinatumomab and it is likely that drug procurement costs (based on the list prices of the two drugs) will also result in inotuzumab costing less than blinatumomab. As inotuzumab results in

	higher rates of CR and SCT than combination chemotherapy at 1st relapse, it is likely to become the treatment of choice at this place in the treatment pathway. NHS England notes that that at the time of the NICE scope, NICE stated that the comparators for T-L should be 'established clinical management without T-L'. NICE did list the inotuzumab appraisal in the March 2018 scope as an appraisal in development. Although NHS England recognises that inotuzumab is not yet in August 2018 a part of 'established clinical management', it will become so in the very near future given its obvious practical advantages. For the much larger T-L eligible populations of relapsed post-SCT and in 2nd or further relapse that have not had SCT, the comparator options are currently the same treatments in these 2 places in the treatment pathway and depend on what has been used previously – if chemotherapy is used at 1st relapse, then the comparator at 2nd relapse would be blinatumomab (though shortly to be inotuzumab); if blinatumomab is used at 1st relapse (and shortly to be replaced by inotuzumab), then the comparator for 2nd relapse would be chemotherapy, the most commonly used regimen being FLA(G)-IDA or the ALLR3 protocol (which is similar to FLA-IDA although given for longer) or the combination of clofarabine, cyclophosphamide and etoposide. As has been stated above, treatment for 1st line relapse is likely to become inotuzumab in the near future and hence these same 2 options of blinatumomab and FLA(G)-IDA apply as comparators for T-L. There is little data on the use of blinatumomab after previous inotuzumab although there is no biologically plausible reason as to why blinatumomab should not be active. However this lack of evidence may affect the choice of treatment.
Is blinatumomab an appropriate comparator to tisagenlecleucel-T for relapsed disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	See above

Question 4: Is it appropriate to use clofarabine as a proxy for the efficacy of FLA-IDA (that is salvage chemotherapy)?	
Is clofarabine used in clinical practice in the NHS in England?	Clofarabine is used but in combination chemotherapy ie not as monotherapy.
Is there any evidence to support the equivalence of FLA-IDA and clofarabine?	NHS England notes that Novartis used clofarabine monotherapy data as the proxy for combination chemotherapy with FLA-IDA. The clofarabine data was use of clofarabine monotherapy, not combination treatment (single-agent cytotoxic chemotherapy is very rarely used in acute leukaemia). The clofarabine monotherapy data was old, the first patient being treated in 2002 and the data cut off was in September 2004. Supportive care has changed much since 2002-2004 with significantly improved outcomes, including in the access to and the speed of access to SCT donors. This therefore means that the outcomes in the clofarabine monotherapy dataset are likely to be inferior to those of the combination FLA-IDA given in in a more contemporaneous time. The indirect comparison of the pooled T-L studies with old clofarabine monotherapy data used as a proxy for FLA-IDA is inappropriate as there is more contemporaneous data for FLA-IDA (according to the ERG) with greater numbers of patients and longer median duration of follow-up. The heterogeneity of the data in any indirect comparisons of T-L with chemotherapy and also with blinatumomab is noteworthy.
Question 5: Long term usage and costs of IVIG treatment - real world experience	
Would people younger than 18 years of age require continued IVIG treatment and for how long?	A significant side-effect is hypogammaglobulinaemia. B-cell ablation is a pharmacodynamic measure of successful treatment with CAR-T cell products directed against leukaemia of B-cell origin. Loss of circulating B-cells and consequent drastic falls in serum immunoglobulin (Ig) levels, also known as agammaglobulinaemia, is a predictable on-target off-tumour effect of T-L. The pivotal study on T-L in children and young adults with refractory acute lymphoblastic leukaemia (Maude et al. New Eng J Med 2018;378:439-48) showed that all patients

	responding to CAR-T cells developed B-cell aplasia and *most* of these 75 patients (exact number not specified) received IVIg. The probability of B cell recovery was [redacted] at 12 months but NHS England notes that this figure did not change at [redacted] months (albeit based on small numbers). From the point of view of a clinician looking after these highly immunosuppressed patients who all undergo conditioning chemotherapy prior to CAR-T cell treatment, there is bound to be considerable anxiety associated with merely observing a patient with no circulating B cells and Ig, as opposed to intervening with prophylactic Ig. Until there is solid longitudinal data on the infection risks associated with CAR-T cell associated agammaglobulinaemia, there is bound to be great and clinically justifiable pressure to use prophylactic Ig. Whilst it is not expected that every patient who receives a B-cell directed CAR-T cell treatment will require IVIg, it is predicted that the majority of responders to CAR-T cells will do so. For the purposes of costing IVIg requirements, long term follow up data on the proportion of patients who developed B-cell aplasia and low Igs as a consequence of CAR-T cell therapy is required. Until that is known, a pragmatic estimate of that up to 50% of responders will require IVIg (until B cell aplasia recovers) for a period of 12-24 months would not be unreasonable. As regards route of delivery, both intravenous Ig (IVIg) and subcutaneous Ig (SCIg) would be equally efficacious. Given that CAR-T cell therapy will be limited to major haematology centres, it is expected that the majority of those patients requiring Ig will be able to undergo training for home administration of SCIg. IVIg and SCIg are costly interventions and thus could have a significant impact on the mean cost of the supportive care that has to be wrapped around each patient who responds to T-L.

Would people aged 18-25 years require continued IVIG treatment and for how long?	

Thank you for your time.

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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 [ID1167]

Document B
Company evidence submission

May 2018

File name	Version	Contains confidential information	Date
Novartis_ID1167_Document B_AIC_CIC_FINAL	N/A	Yes	18th May 2018

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

List of tables

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukaemia
BCR-ABL	Breakpoint cluster region Abelson
BIC	Bayesian information criterion
BM	Bone marrow
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
CAR	Chimeric antigen receptor
CD3	Cluster of differentiation 3
CD19	Cluster of differentiation 19
CHMP	Committee for Medicinal Products for Human Use
CHRI	Child Health Ratings Inventories
CI	Confidence interval
CLL	Chronic lymphoblastic leukaemia
CNS	Central nervous system
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
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of remission
DP	Destination protocol
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
EFS	Event-free survival
EGP	Economic Guidance Panel
EMA	European Medicines Agency
eMIT	Electronic market information tool
EPAR	European public assessment report
EQ-5D-3L	EuroQoL 5-Dimensions 3-Levels
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FLA-IDA	Fludarabine, cytarabine and idarubicin
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life

HUI2	Health Utilities Index 2
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient data
IRC	Independent Review Committee
iv	Intravenous
IVIG	Intravenous immunoglobulin
LD	Lymphodepleting
LY	Life year
LYG	Life years gained
MAIC	Matched-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MLL	Mixed lineage leukaemia
MRD	Minimal residual disease
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reached/not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PBMC	Peripheral blood mononuclear cells
pCODR	pan-Canadian Oncology Drug Review
PD	Progressive disease
PedsQL	Paediatric Quality of Life questionnaire
PFS	Progression-free survival
Ph+ve	Philadelphia chromosome positive
PLL	Prolymphocytic leukaemia
PLN	Polish zloty
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-adjusted life year
RBC	Red blood cell
RCT	Randomised controlled trial
RFS	Relapse-free survival
r/r	Relapsed/refractory
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	36-item short form survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TBI	Total body irradiation

TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WBC	White blood cell

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

B.1.1 Decision problem

This submission covers the full anticipated marketing authorisation for the technology tisagenlecleucel (Kymriah™) 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, hereafter referred to as relapsed/refractory (r/r) B-cell ALL.

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 3 to 25 years with relapsed or refractory B-cell ALL.	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.	The patient population addressed within this submission also includes patients aged 0–3, in line with the anticipated licensed indication for tisagenlecleucel in 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.
Intervention	Tisagenlecleucel.	Tisagenlecleucel.	N/A – in line with the final NICE scope.
Comparator(s)	Established clinical management without tisagenlecleucel at one of the following lines of therapy: • Bone marrow relapse o following second or greater bone marrow relapse, o following any bone marrow relapse, within 6 months or less, after allogeneic stem cell transplant (allo-SCT)	• Salvage chemotherapy (specifically, FLA-IDA [fludarabine, cytarabine and idarubicin]) • Blinatumomab	It should be noted that the draft SmPC for tisagenlecleucel states that it is not recommended for patients to receive tisagenlecleucel within 4 months of undergoing an allo-SCT.[1] As such, where NICE have included the following line of therapy: *following any bone marrow relapse, within 6 months or less, after allo-SCT,* Novartis have considered this to instead be: *following any bone marrow relapse, at least 4 months or more after allo-SCT.* The comparators included within this submission represent established clinical management without tisagenlecleucel and are therefore in line with the final NICE scope for patients at the following lines of therapy: • Bone marrow relapse o following second or greater bone marrow relapse,

	• Primary refractory disease • Philadelphia chromosome positive (ph+ve) ALL o intolerant to or having failed 2 lines of TKI therapy (or where TKI therapy is contraindicated), o patients ineligible for allo-SCT		o following any bone marrow relapse, at least 4 months or more, after allo-SCT • Primary refractory disease In the absence of any national or European guidelines, and having consulted with several UK clinical experts, paediatric and young adult patients up to 25 years of age with r/r B-cell ALL that is refractory (either primary refractory, or chemo-refractory post-therapy received in first relapse), in relapse post-transplant, or in second or later relapse currently receive either salvage chemotherapy (specifically FLA-IDA [fludarabine, cytarabine and idarubicin]) or blinatumomab in UK clinical practice.[2] Whilst there may be differences in the *order* in which these therapies are tried for patients with either relapsed or refractory disease, based on feedback from UK clinical experts, the most relevant comparator(s) are the same for all patient groups covered by the anticipated licensed indication.[2] Therefore, these same therapies (salvage chemotherapy [FLA-IDA] and blinatumomab) represent comparators for all eligible patients within the indicated patient population of this appraisal. The proportion of patients with Ph+ve ALL within the eligible patient population will constitute a small minority (<3%)[3] and therefore tyrosine kinase inhibitors (TKIs) are not considered to represent relevant comparators to this submission. Furthermore, given the eligibility criteria of the tisagenlecleucel clinical trials, patients had to have tried and failed two prior lines of TKI therapy, and feedback from UK clinical experts is that the use of a 3rd TKI does not constitute standard practice.[2] There is also a distinct lack of data in the Ph+ve ALL population, for both tisagenlecleucel and the relevant comparators in this indication, and therefore it was not feasible for Novartis to present a robust comparison for this subgroup and as such, no comparison has been presented within this submission.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival (including relapse-free and	• Overall survival • Event-free survival • Relapse-free survival • Response rate (including minimal residual disease	N/A – in line with the final NICE scope.

	event-free survival) • Response rate (including minimal residual disease and haematological responses and complete remission) • Rate of allogeneic stem cell transplant (allo-SCT) • Adverse effects of treatment • Health-related quality of life	and haematological responses and complete remission) • Rate of allo-SCT • Adverse effects of treatment • Health-related quality of life (specifically the EQ-5D-3L and PedsQL)	
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	• The cost-effectiveness of treatments is expressed in terms of the incremental cost per QALY • A lifetime time horizon has been adopted • Costs are considered from the perspective of the NHS and PSS • The availability of a PAS has been included for tisagenlecleucel	N/A – in line with the final NICE scope.

	or comparator technologies will be taken into account		

Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic stem cell transplantation; EQ-5D-3L: EuroQoL 5-dimensions 3-levels; FLA-IDA: fludarabine, cytarabine, idarubicin; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PAS: Patient access scheme; PedsQL: Paediatric Quality of Life questionnaire; Ph+ve: Philadelphia Chromosome positive; PSS: Personal and Social Services; QALY: quality-adjusted life year; SmPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor; UK: United Kingdom.
Source: NICE Final Scope for ID1167.[4]

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with the technology, tisagenlecleucel, for the treatment of paediatric and young adult patients with r/r B-cell ALL is presented in Table 2.

Table 2: Technology being appraised

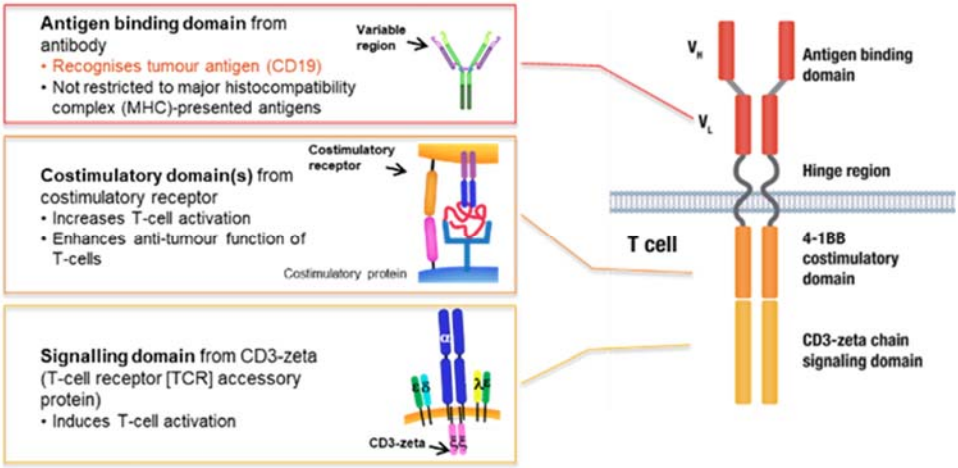
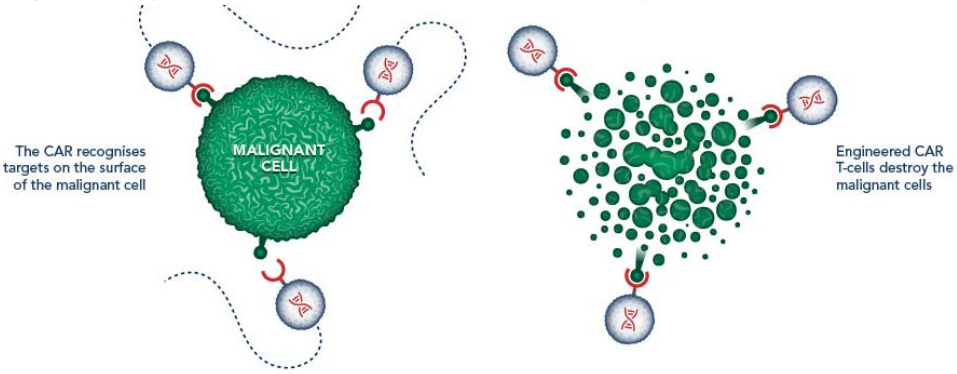
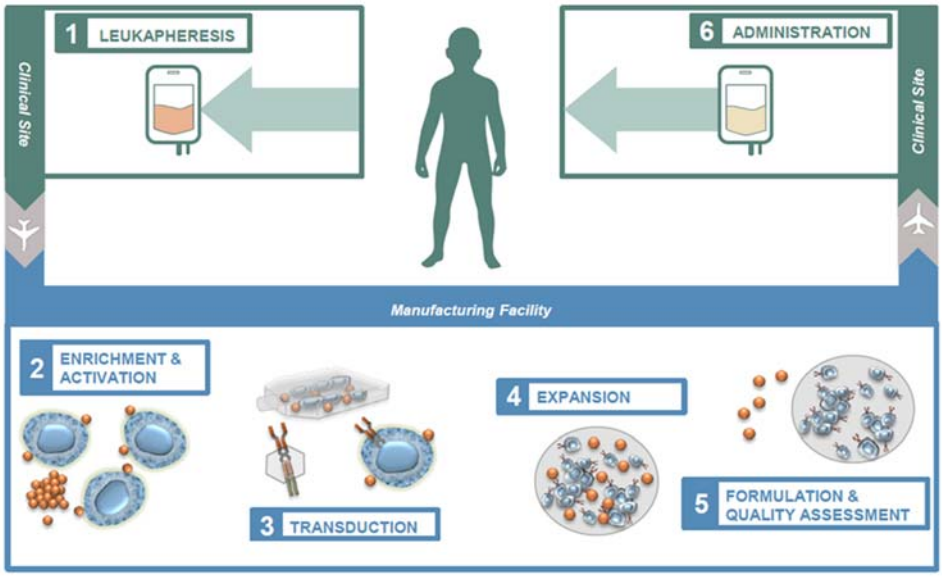
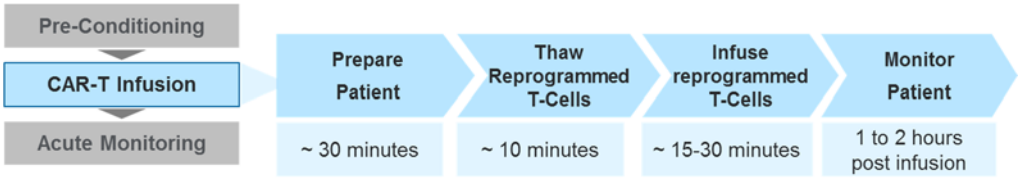
UK approved name and brand name	Tisagenlecleucel (Kymriah™).
Mechanism of action	Tisagenlecleucel is a genetically modified chimeric antigen receptor (CAR)-based autologous immunocellular therapy administered as a single intravenous (iv) infusion for the treatment of r/r B-cell ALL that utilises similar mechanisms to that of cytotoxic T-cells to kill leukaemic cells and thereafter maintain ongoing anti-tumour surveillance. 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.[5] **Figure 1: Domains of the chimeric antigen receptor construct of tisagenlecleucel**  **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.[6] Expression of CD19 is largely restricted to B lineage cells;[5] therefore, CD19 represents an attractive immunotherapy target in ALL as it is present on leukaemic B-cells but is not found on bone marrow stem cells or other healthy tissues. Tisagenlecleucel is therefore able to target tumour cells whilst largely sparing non-cancerous cells from cytotoxicity, consequently limiting systemic effects.[7] Once tisagenlecleucel binds to CD19-positive leukaemic cells,[5] the CAR-T-cell becomes activated and the cytotoxic potential of these cells is realised (see Figure 2). Death of leukaemic 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.[8] Ligation of the CAR-T receptor also leads to CAR-T-cell proliferation.[8]

	Figure 2: Cytotoxic mechanism of CAR-T therapy  **Source:** Novartis Pharmaceuticals UK Ltd. In contrast to the therapies currently available for patients with r/r B-cell ALL, the mechanism of action of tisagenlecleucel is entirely novel. CAR T cells have so far been detected in the peripheral blood of patients up to 784 days post infusion.[1] 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 is the first in this class of CAR-T therapy for the treatment of r/r B-cell ALL, representing a paradigm-shift in the treatment approach for this aggressive and potentially fatal disease that offers paediatric and young adult patients the potential for a cure with just a single infusion.
Marketing authorisation/ CE mark status	On 30th August 2017, tisagenlecleucel received regulatory approval from the Food and Drug Administration (FDA) in the US for the treatment of patients up to age 25 years with B-cell ALL that is refractory or in second or later relapse.[9] This was the first instance of FDA approval of a CAR-T therapy worldwide, demonstrating the revolutionary nature of tisagenlecleucel in this indication and the introduction of a pioneering treatment approach for paediatric and young adult patients with r/r B-cell ALL.[9] Tisagenlecleucel does not yet hold an EU marketing authorisation for the treatment of paediatric and young adult patients with r/r B-cell ALL. A marketing authorisation application for tisagenlecleucel in this indication was submitted to the European Medicines Agency (EMA) on 6th November 2017 and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in May 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated EU marketing authorisation wording for tisagenlecleucel in this indication is: "Tisagenlecleucel (Kymriah™) is a CD19-directed autologous immunotherapy indicated for the treatment of paediatric and young adult patients up to 25 years of age of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse." Patients with hypersensitivity to the active substance or any of the excipients listed in Section 6.1 of the SmPC are contraindicated. Furthermore, infusions of tisagenlecleucel should be withheld until resolution of any of the following conditions: • Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies • Active uncontrolled infection • Active chronic graft-versus-host disease (GVHD) • Significant clinical worsening of leukaemia burden or lymphoma following lymphodepleting chemotherapy Full details are provided in the draft SmPC provided in the reference pack.[1]

Method of administration and dosage	**Method of administration** In contrast to typical small molecule or biologic products, each dose of tisagenlecleucel is specifically tailored to, and manufactured for, each patient using the patient's own blood cells, representing an entirely novel and personalised approach to the manufacturing, logistics and administration of treatment for paediatric and young adult patients with r/r B-cell ALL. The multistep supply chain process is summarised below (and in Figure 3):[5, 10, 11] • **Step 1:** The patient is admitted to hospital and their mononuclear cells are obtained by a process known as leukapheresis. • **Step 2:** The patient's cells are then cryopreserved in the vapour phase of liquid nitrogen and shipped to a manufacturing facility in the US using a dedicated courier service. • **Step 3:** At the manufacturing facility, the mononuclear cells are thawed and enriched for T cells. The T cells are activated with antibody-coated beads and genetically transduced using a lentiviral vector (inactive virus) containing the anti-CD19 CAR transgene. • **Step 4:** The CAR-T-cells then undergo ex vivo expansion on antibody-coated beads • **Step 5:** The CAR-T-cells undergo formulation and a strict quality assessment before being released, cryopreserved and shipped. As an autologous (patient specific) product entering the EU, each individual therapy then requires a separate certification and batch release appropriate to the European regulations governing genetically modified advanced therapy medicinal products. Following certification, the product is sent back to the hospital where it can be stored in liquid nitrogen for up to 9 months until the treating centre / staff are ready to administer, and the patient is ready to receive treatment. • **Step 6:** The patient can receive bridging chemotherapy between leukapheresis and infusion at the discretion of the treating physician. Prior to tisagenlecleucel infusion the patient receives a preparative low dose lymphodepleting regimen. The CAR-T-cells are then thawed and reinfused into the patient as a one-time single-dose of tisagenlecleucel. According to the SmPC, tisagenlecleucel infusions should be administered 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 and during the recovery period. **Figure 3: Summary of the administration process for tisagenlecleucel**  **Source:** Novartis Pharmaceuticals UK Ltd.

	Lymphodepleting chemotherapy: • 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.*[1] **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.[1] A summary of the tisagenlecleucel infusion process is presented in Figure 4 below. **Figure 4: Tisagenlecleucel infusion process**  **Abbreviations:** CAR-T: chimeric antigen receptor T-cell. **Source:** Novartis Pharmaceuticals UK Ltd.
Additional tests or investigations	Prior to infusion the HBV, HCV and HIV status of the patient should be known.
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 (if applicable)	A confidential patient access scheme (PAS) discount of [redacted] off the tisagenlecleucel list price is currently under discussion with NHS England. Results within this submission are presented with both tisagenlecleucel at list price and PAS 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; FDA: Food and Drug Administration; GVHD: graft versus host disease; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: juman immunodeficiency virus; iv: intravenous; MHC: major histocompatibility complex; r/r: relapsed/refractory; 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 a rare but aggressive haematological malignancy and yet one of the most common cancers to affect children and young adults.[12] It is characterised by the overproduction and accumulation of immature white blood cells (lymphoblasts) which causes the inhibition of normal blood cell production and function and eventually leads to the infiltration of lymphoblasts to other organs.[12]
- Whilst remission rates to conventional first-line chemotherapy are high, approximately 20% of patients will experience disease relapse, and a further 36% of patients will experience a second relapse, with disease prognosis worsening with each subsequent relapse.
- For paediatric and young adult patients experiencing a second or greater relapse the prognosis is dismal; median OS ranges from 3–7.5 months and current treatment options are associated with poor remission rates, reduced HRQoL, as well as medical and psychosocial consequences.[13, 14] For these patients, there is a critical unmet need for a novel therapy that can provide improved remission rates and the potential for a cure.
- 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, emotional and financial pressures.[15, 16]

Epidemiology

- ALL is a rare disease overall, with only 832 new cases diagnosed in the UK in 2015.[17] However, in contrast to many other cancer types, ALL has the highest incidence in children and young adults; approximately half of these cases are in patients aged<25 years and as such, ALL represents a major contribution to the burden of paediatric cancer in the UK.

Clinical pathway of care

- There are currently no paediatric or young-adult specific national clinical guidelines for the treatment of ALL in the UK.
- Based on feedback from UK clinical experts, ALL patients <18 years who experience a *first relapse* in the UK are typically treated according to the ALLR3 trial protocol, with older patients (aged 18–25 years) generally receiving blinatumomab with the aim of bridging to allo-SCT (if patients are eligible).
- If a *second relapse* occurs, treatment options are severely limited and prognosis is extremely poor, particularly if relapse occurs following allo-SCT. The vast majority of patients are treated with either salvage chemotherapy (specifically FLA-IDA) or blinatumomab (if not received previously) in this setting, with a minority of patients enrolling on to investigational clinical trials.
- Tisagenlecleucel is anticipated to be licensed 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 this setting, tisagenlecleucel offers a revolutionary and individualised approach to meet the critical unmet need in r/r B-cell ALL with just a single infusion, providing 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.[12] 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.[18, 19]

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.[12, 20] B-cell ALL is considerably more common than T-cell ALL, representing 80–85% of cases in children.[21] 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 and is notoriously harder to treat than Ph-ve ALL.[20, 22] The anticipated licence for tisagenlecleucel covers all B-cell ALL patients regardless of Ph chromosome disease status.

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.[23] 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.[24, 25] As an aggressive disease, if left untreated, ALL is usually fatal within a few weeks or months.[23]

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).[26] 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%.[27, 28] However, despite these high remission rates, approximately 20% of patients will subsequently experience disease relapse, and the majority of relapses occur within two years of first-line treatment.[25, 29]

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.[2] Second CR rates with chemotherapy for patients who experience a first relapse are still reasonably high, and can range from 71–93%.[3] 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 are reported to be 44%, 27% and 12% respectively, demonstrating a substantial decrease in responsiveness with every treatment failure.[30] The proportion of patients estimated to experience a second relapse is 36%. 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).[31] 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.[3]

Burden of disease

The burden of disease for ALL is associated with significant patient and parent/caregiver impact.[15, 16, 32, 33] Patients with r/r B-cell ALL have an extremely poor prognosis and this is exacerbated further with each subsequent relapse.[30] Median OS with current treatment in the r/r setting ranges from less than 3 months to 7.5 months.[34, 35] Therefore, and 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.[32] 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.[32, 33]

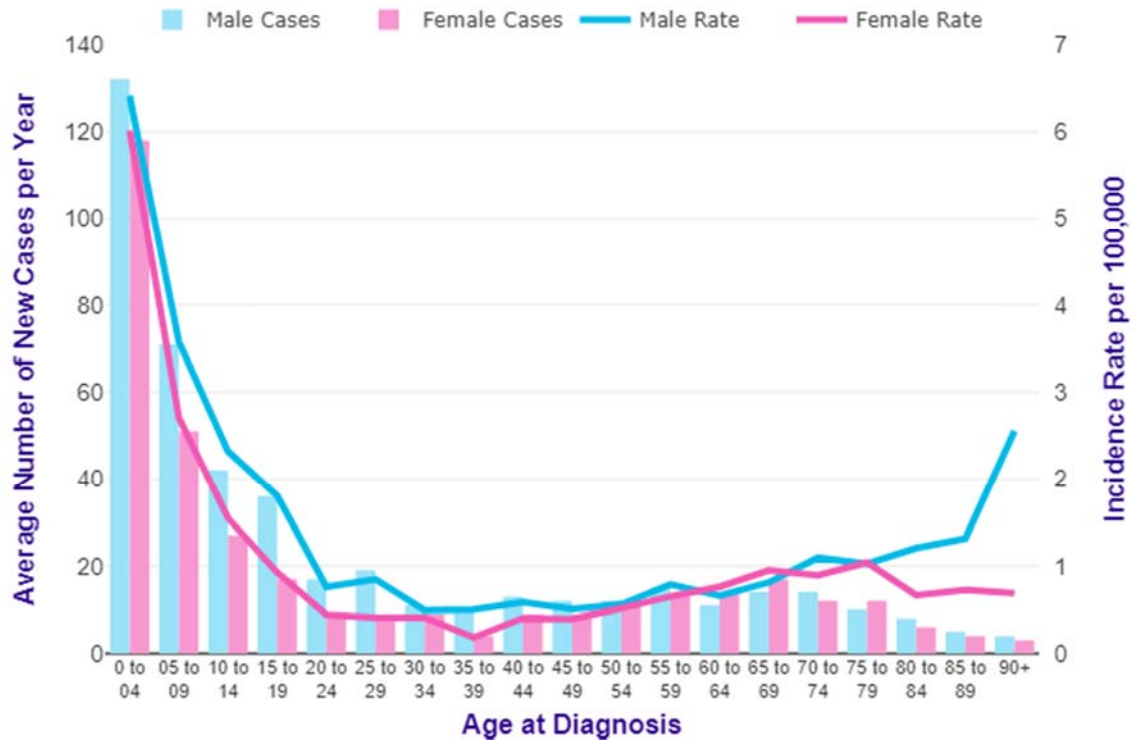
As a disease that affects children and young adults, who in some cases are very young, r/r B-cell ALL has a substantial impact on parents and caregivers, who can experience significant psychological distress, depression, anxiety, stress and emotional pressures.[15, 16] Moreover, the economic burden of 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.[36] The burden of disease is therefore not only felt by patients themselves, but has a dramatic and widespread impact on entire families and their wider 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 therefore help to alleviate this parent and caregiver burden, improving the quality of life of children and young adults affected by ALL.

Incidence of ALL in children and young adults

ALL is considered a rare disease, with just 832 new cases of ALL diagnosed in the UK in 2015, accounting for less than 1% of all new cancer diagnoses in adults and children in the UK.[17] 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 5).[37] Of the average 811 new cases of ALL diagnosed in the UK each year between 2013–2015, 520 cases (64%) were in patients aged 0 to 24 years.[17] 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 almost 80% of all childhood leukaemias and 25% of all childhood cancers.[12]

Figure 5: Average number of new cases of ALL per year and age-specific incidence rates in the UK (2013-2015)



Abbreviations: ALL: acute lymphoblastic leukaemia; UK: United Kingdom.
Source: Cancer Research UK.[37]

B.1.3.2 Clinical pathway of care

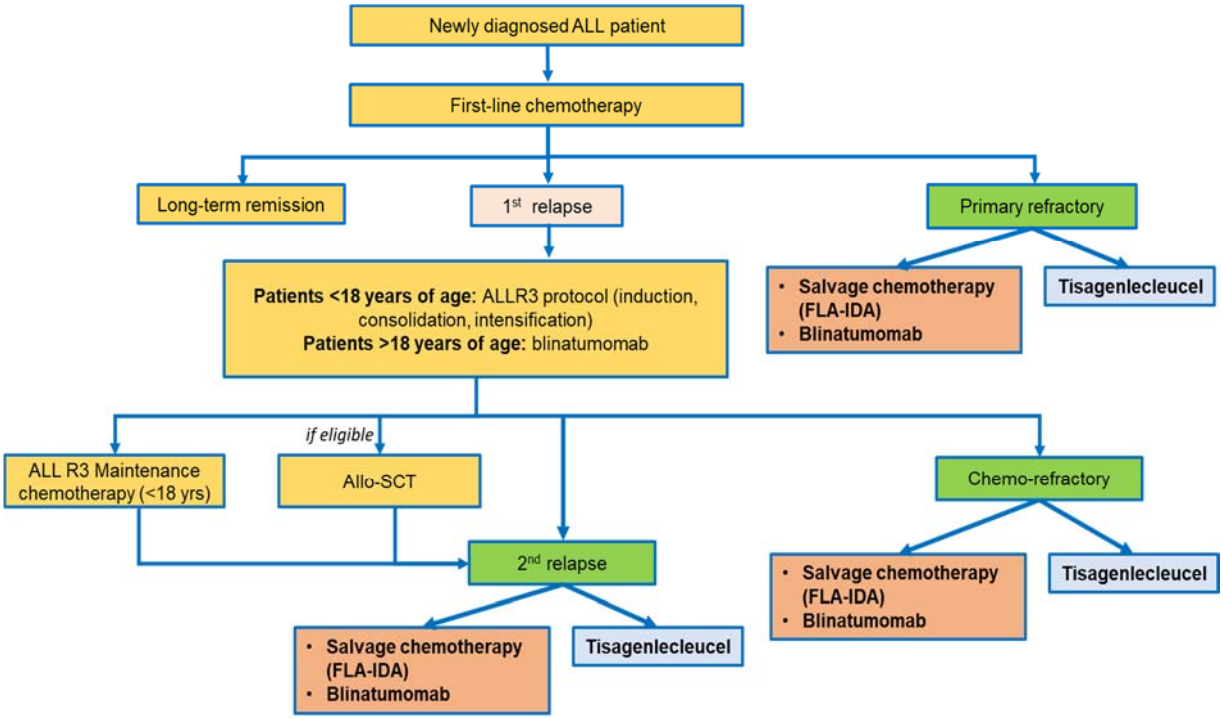
Tisagenlecleucel is anticipated to be licensed for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse.

Whilst 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, there are currently no paediatric or young-adult specific national clinical guidelines for the treatment of ALL in the UK.[38, 39]

The NCCN guidelines are not followed by UK clinical experts and many paediatric and young adult patients with r/r B-cell ALL in the UK are typically entered into experimental clinical trials if possible; for patients who do not enter a clinical trial, treatment is guided by clinical trial protocols, where available, and by clinician choice.[2]

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 6 based on feedback from several clinical experts in the UK.[2]

Figure 6: Treatment pathway for ALL in the UK with the potential positioning of tisagenlecleucel



Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: stem cell transplantation; FLA-IDA: fludarabine, cytarabine and idarubicin.
Source: UK expert clinician feedback.[2]

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.[26] 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 cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine.[40]

Relapsed disease

Despite high CR rates that can be achieved with first-line chemotherapy, approximately 20% of patients will experience relapsed disease following CR from first-line chemotherapy.[28] Patients under the age of 18 years who experience a first relapse or refractory disease in the UK are typically treated according to the ALLR3 protocol, an international collaborative clinical trial protocol developed by the Childhood Leukaemia Working Party in the UK.[41] The ALLR3 protocol varies according to patient risk and contains three phases; induction, consolidation and intensification. For patients who achieve a CR to ALLR3 induction therapy, some patients will receive maintenance chemotherapy and some will go on to receive an allo-SCT (if eligible) (see Figure 6).[2, 41]

Patients over the age of 18 who experience a first relapse in the UK are typically treated with blinatumomab, with the aim of bridging to allo-SCT (if patients are eligible).[2]

For patients who then experience a second relapse following maintenance chemotherapy or allo-SCT, or relapse before being able to receive an allo-SCT, treatment options are severely limited, and an established protocol of care does not exist. The only therapy licensed by the EMA for the

treatment of r/r B-cell ALL in paediatric/young adult patients who have received at least two prior regimens is clofarabine; however, the consensus from UK clinical experts is that clofarabine is rarely used, if at all, in the UK due to toxicity.[2, 42] The vast majority of these patients typically receive treatment with either salvage chemotherapy (specifically the FLA-IDA regimen: fludarabine, cytarabine and idarubicin) or blinatumomab (if not received previously) (see Figure 6).

Blinatumomab is licensed by the EMA and NICE approved for the treatment of adults with r/r B-cell ALL.[43, 44] Whilst it is yet to be licensed in the paediatric population, due to the NHS England national commissioning policy, blinatumomab is currently also available for paediatric patients with r/r B-cell ALL in England.[45] However, feedback from UK clinical experts is that many patients are in fact treated with blinatumomab earlier on in the pathway following a first relapse with the aim of bridging to allo-SCT.[2] This is also in line with the recommendations from NICE for blinatumomab in the adult population.[44] As such, given the earlier use of blinatumomab, some clinical experts would view salvage chemotherapy (FLA-IDA) as their preferred treatment option following a second relapse, or relapse post allo-SCT.[2]

Proposed positioning of tisagenlecleucel

Tisagenlecleucel is anticipated to be 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. Therefore, within the context of this appraisal, salvage chemotherapy (FLA-IDA) and blinatumomab represent the most relevant comparators to tisagenlecleucel within the treatment pathway for paediatric and young adult patients who have r/r B-cell ALL.

Despite its use, no clinical evidence exists for the efficacy of FLA-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 FLA-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%.[2, 34] 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.[35, 46] 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).[35, 46]

Therefore, there is a critical unmet need for a novel therapy that can provide 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 [redacted] patients. Across all three clinical trials, tisagenlecleucel has demonstrated consistent, clinically meaningful efficacy with high remission rates, deep molecular responses, and durable remissions. 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.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The efficacy of tisagenlecleucel has been established in three clinical trials (ELIANA, ENSIGN and B2101J) involving [redacted] paediatric and young adult patients with r/r B-cell ALL.[47-49]
- The primary efficacy endpoint of ELIANA was met, with an independent review committee (IRC)-assessed overall remission rate (ORR) of [redacted] (95% confidence Interval [CI]: [redacted]) within 3 months after infusion.[47] Similarly high remission rates were achieved in ENSIGN (ORR of 69.0%) and B2101J (ORR of [redacted]).[48, 49]
- 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.[31] Results for this endpoint ([redacted]; 95% CI: [redacted]) demonstrated deep remissions in [redacted] of patients, and confirmed the observed clinical benefit seen with the primary endpoint.[47] Similarly high ORRs with MRD-negative bone marrow remissions were reported in ENSIGN (64.3%), and B2101J ([redacted]).[48, 49]
- In the majority of patients, durable remissions were observed across all three trials.[47-49] The rate of event-free survival (EFS) at 12 months was [redacted] in ELIANA, [redacted] in ENSIGN and [redacted] in B2101J.[47-49]
- Promising survival outcomes were observed across all three trials.[47-49] The probability of survival at Month 12 was [redacted] in ELIANA, 62.6% in ENSIGN, and [redacted] in B2101J.[47-49] Median OS in B2101J, the trial with the longest follow-up, was [redacted] months.[49]
- In ELIANA, two different HRQoL tools demonstrated improvements in patient-reported outcomes at 3 and 6 months following infusion further supporting the clinical benefit of tisagenlecleucel.[50]

Summary of the results from the indirect treatment comparison

- Given the absence of a head-to-head clinical trial versus the relevant comparators to this appraisal, a matched-adjusted indirect comparison (MAIC) was conducted for OS versus salvage chemotherapy (using clofarabine monotherapy as a proxy for the efficacy of FLA-IDA) and blinatumomab.
- After adjusting for population differences via the MAIC, tisagenlecleucel was estimated to have statistically superior OS over both clofarabine monotherapy (a proxy for salvage chemotherapy) and blinatumomab. Full details of the MAIC are presented in Section B.2.8.

Summary of safety results for tisagenlecleucel

- The safety profile of tisagenlecleucel has been well characterised and was consistent across all three trials.[47-49] Full details of the safety profile of tisagenlecleucel in paediatric and young adult patients with r/r B-cell ALL are presented in Section B.2.10.

B.2.1 Identification and selection of relevant studies

An SLR was conducted in March 2018 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 77 publications, reporting on 66 unique clinical trials. Of these, 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).[51-56]

B.2.2 List of relevant clinical effectiveness evidence

Three clinical trials were identified in the SLR that provide 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).

ELIANA is an ongoing, 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.[57] Data from ELIANA have been published by Maude *et al.* (2018) based on a median 13.1 months of follow up;[54] 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 ELIANA Clinical Study Report (CSR; data cut-off 31st Dec 2017 representing a median [redacted] follow-up).[47]

ENSIGN is an ongoing, 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.[58] Data from ENSIGN have been published by Maude *et al.* (2016) representing a median 6.4 months of follow up;[55] 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 (data cut-off 6th Oct 2017 representing a median [redacted] of follow up).[48]

B2101J was the first trial to be conducted in tisagenlecleucel and is an ongoing, 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.[59] Data from B2101J have been published by Maude *et al.* (2014) representing a median 7 months of follow up;[60] 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 (data cut-off 30th Jan 2017 representing a median [redacted] of follow up).[49]

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

Table 3: Clinical effectiveness evidence

Trial	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Study design	International, multicentre, phase II, single-arm, open-label study to assess efficacy and safety	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. [redacted] **(enrolled);** [redacted] **(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=73 (enrolled); N=58 (infused)**	Paediatric and young adult patients up to 24 years of age (range 1–24 years) with chemotherapy resistant or refractory CD19+ B-cell leukaemia and lymphoma.[a] [redacted] **(enrolled);** [redacted] **(infused) [all non-CNS3 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)[b]	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)[b]	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)
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	Yes	Yes
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

[a]Note as of the respective data cuts presented within this submission, no patients with lymphoma had been infused with tisagenlecleucel and therefore 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 CTL019 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 CTL019 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: 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: United States.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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.[47-49]

ELIANA trial design

ELIANA is an ongoing, international, multicentre, phase II, single-arm, open-label study.[57] 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 allogeneic allo-SCT, or otherwise ineligible for allogeneic allo-SCT were enrolled in the trial.[57]

A schematic of the ELIANA trial design is presented in Figure 7. The trial consists of several sequential phases: screening, pre-treatment, treatment and primary follow-up, secondary follow-up and survival follow-up.[47]

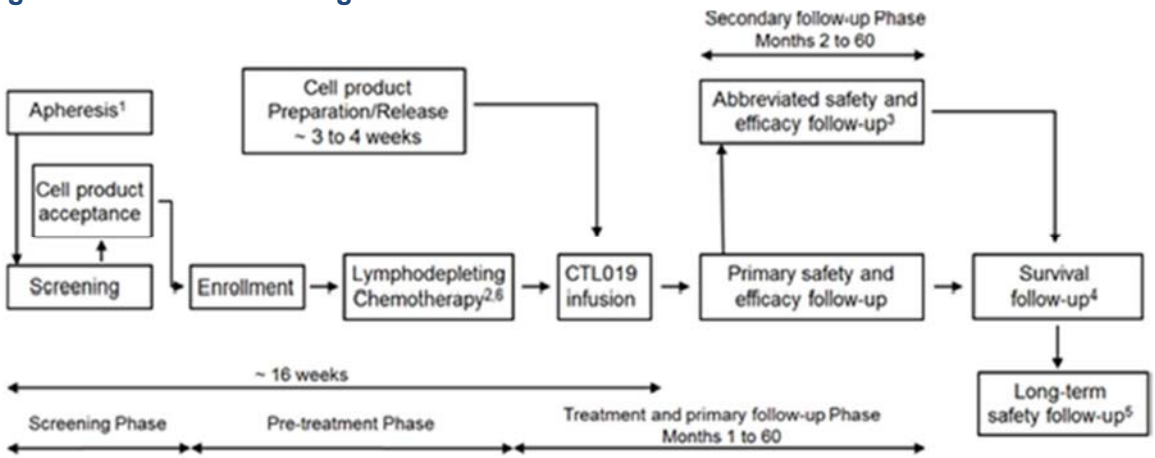
Screening and pre-treatment: Patients were screened for eligibility following leukapheresis. Eligible patients were then enrolled in the trial, and treated with bridging chemotherapy (where appropriate) followed by lymphodepleting chemotherapy 2–14 days prior to tisagenlecleucel infusion.

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 7: 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; [6]To be completed 2–14 days prior to tisagenlecleucel infusion: fludarabine (30 mg/m^2 iv daily for 4 doses) plus cyclophosphamide (500 mg/m^2 iv daily for 2 doses).
Source: ELIANA CSR (31st Dec 2017).[47]

ENSIGN trial design

ENSIGN is an ongoing, international, 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.[58] 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 allogeneic allo-SCT, or otherwise ineligible for allogeneic allo-SCT were enrolled in the trial.[48] As of the data cut-off date presented within this submission (6th Oct 2017), no patients with lymphoblastic lymphoma had been infused with tisagenlecleucel and therefore the population treated and subsequently analysed within this submission exclusively includes patients with r/r B-cell ALL.

A schematic of the ENSIGN trial design is presented in Figure 8. The trial consists of several sequential phases: screening, pre-treatment, treatment and primary follow-up, secondary follow-up and survival follow-up.[48]

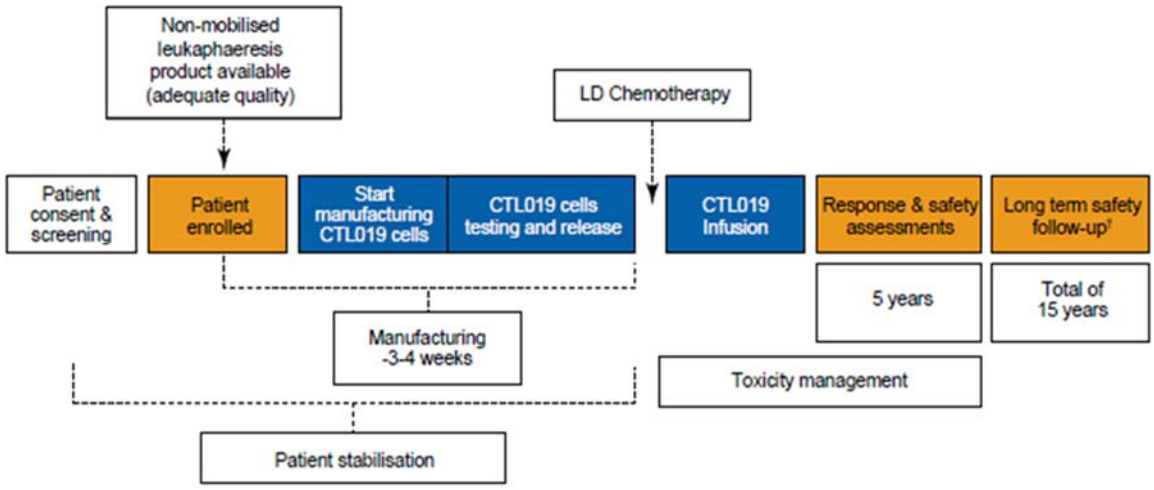
Screening and pre-treatment: Patients were screened for eligibility following leukapheresis. Eligible patients were then enrolled in the trial, and treated with bridging chemotherapy (where appropriate) followed by lymphodepleting chemotherapy 2–14 days prior to tisagenlecleucel infusion.

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 for up to 5 years.

Survival and long-term safety follow-up: The survival follow-up period is to collect survival data 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 8: ENSIGN trial design



Abbreviations: LD: lymphodepleting chemotherapy.
Source: ENSIGN CSR (6th Oct 2017).[48]

B2101J trial

B2101J is an ongoing, single centre, phase I/IIa, single-arm, open-label study.[59] Paediatric and young adult patients with r/r B-cell ALL who were treatment refractory, relapsed after allogeneic allo-SCT, or were otherwise ineligible for allogeneic allo-SCT were enrolled in the trial.[59] 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.[61]

A schematic of the B2101J trial design is presented in Figure 9. The trial consists of several sequential phases: screening, treatment (consisting of apheresis, cytoreductive chemotherapy and tisagenlecleucel administration) and follow-up.[49]

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.

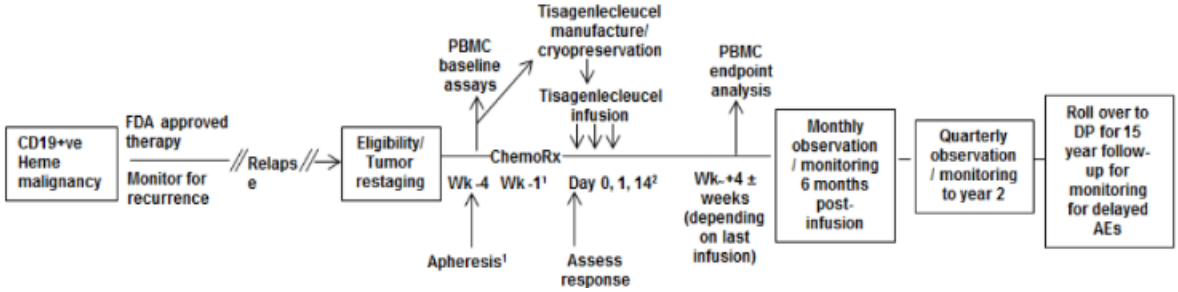
Treatment and primary follow-up: In B2101J, tisagenlecleucel infusion was administered in a dose-escalated manner, a minimum of 1–5 days after the completion of cytoreductive chemotherapy. After tisagenlecleucel infusion, patients entered the primary follow-up period, during which efficacy was assessed 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 9: 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 (30th Jan 2017).[49]

B.2.3.2 Trial methodology

A summary of the methodology of ELIANA, ENSIGN and B2101J is presented in Table 4. 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.[57-59] 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.[48, 50, 59] 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.[48-50]

Table 4: Summary of methodology of studies

Trial	ELIANA (NCT02435849)	ENSIGN (NCT02228096)	B2101J (NCT01626495)
Location	**Clinical sites:** 25 centres across the US, EU, 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 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 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 (age <16 years) performance status ≥ 50 at screening	**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 • Karnofsky (age ≥ 16 years) or Lansky (age <16 years) performance status ≥ 50 at screening	**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 o 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 prior allogeneic allo-SCT if no active GVHD and no immunosuppression • Adequate organ function • Life expectancy >12 weeks

	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 L.	**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 L.	• 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 L.
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 with the first dose of fludarabine).	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 the first dose of fludarabine).	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 **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.[47]	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.[48]	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	• ORR determined by IRC assessment (defined as a best overall response [BOR] of either CR and CRi within 3 months of tisagenlecleucel administration)	• ORR determined by IRC assessment (defined as a BOR of either CR and 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 determined by IRC assessment (defined as a BOR of either CR and CRi within 3 months of tisagenlecleucel administration) (US manufacturing facility only)* • BOR of CR or CRi with MRD negative	• 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 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*	• 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 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

	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.	• 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.	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 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.	Pre-specified subgroup analyses for ORR were performed 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.	Pre-specified subgroup analyses for ORR were performed 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.
Discontinuation of study treatment and premature	• 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	• 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	• 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

patient withdrawal	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	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	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 the 8th April 2015 and is ongoing • 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 31st Dec 2017 data cut-off representing a median [redacted] follow up are presented within this submission**	• The study was initiated on the 14th August 2014 and is ongoing • 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 6th Oct 2017 data cut-off representing a median [redacted] follow up are presented within this submission**	• The study was initiated on 15th March 2012 and is ongoing • 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 30th Jan 2017 data cut-off representing a median [redacted] follow up 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 (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017);[49] ClinicalTrials.gov.[59]

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 5. 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.[47-49]

Table 5: 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			
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: o Ongoing without an event o Lost to follow-up o Withdrew consent o New anticancer therapy o Adequate assessment was no longer available o 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.

Abbreviations: AE: adverse event; BOR: best overall response; CR: complete remission; CRi: complete remission with incomplete blood count recovery; DoR: duration of remission; EFS: event-free survival; ORR: overall remission rate; OS: overall survival; RFS: relapse-free survival; allo-SCT: stem cell transplantation.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

B.2.3.3 Baseline characteristics

The ELIANA trial was initiated on the 8th April 2015 (first patient first visit) and is ongoing. At the time of the data cut-off date presented within this submission (31st Dec 2017), [redacted] patients had been screened, [redacted] patients were enrolled, and [redacted] patients had been treated with tisagenlecleucel.[47] The [redacted] patients who received tisagenlecleucel infusion were aged between [redacted] years of age (mean [redacted] years), with fairly equal gender distribution. The vast majority of patients had a Karnofsky/Lanksy performance status of greater than 70, with a median of [redacted] prior therapies of which [redacted] of patients had failed prior allo-SCT. The majority of patients had relapsed disease ([redacted]) and [redacted] patients had primary refractory ALL.[47]

The ENSIGN trial was initiated on the 14th August 2014 (first patient first visit) and is ongoing. At the time of the data cut-off date presented within this submission (6th Oct 2017), 85 patients had been screened, 73 patients were enrolled, and 58 patients had been treated with tisagenlecleucel.[48] The 58 patients who received tisagenlecleucel infusion were aged between 3 to 25 years of age (mean [redacted] years), with fairly equal gender distribution. All patients had a Karnofsky/Lanksy performance status of at least 50, with a median of 3 prior therapies of which 44.8% of patients had failed prior allo-SCT. The majority of patients had relapsed disease (91.4%) and 8.6% patients had primary refractory ALL.[48]

The B2101J trial was initiated on the 15th March 2012 (first patient first visit) and is ongoing. At the time of the data cut-off date presented within this submission (30th Jan 2017), [redacted] patients were enrolled, and [redacted] patients had been treated with tisagenlecleucel.[49] The [redacted] patients who received tisagenlecleucel infusion were aged between [redacted] years of age (mean [redacted] years), with fairly equal gender distribution. All patients had a Karnofsky/Lanksy performance status of at least 80, [redacted] of patients had failed prior allo-SCT, and [redacted] patients had Ph+ve disease. The majority of patients had relapsed disease ([redacted]) and [redacted] had primary refractory ALL.[49]

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 6. The patient populations of each trial can be considered very 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.[2] Although these trials did not include centres within the UK specifically, other European centres were included, and there was consensus from UK clinical

experts that the patients in all three trials can be considered comparable to the patients likely to be treated with tisagenlecleucel in the UK and this should not affect the applicability of tisagenlecleucel to patients in the UK setting.[2]

Table 6: Baseline characteristics (full analysis set)

Characteristic	ELIANA (full analysis set) (N=[redacted])	ENSIGN (full analysis set) (N=58)	B2101J (full analysis set) (N=[redacted])[a]
Demographics			
Age (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	12.0	[redacted]
Min–Max	[redacted]	3–25	[redacted]
Sex, n (%)			
Female	[redacted]	31 (53.4)	[redacted]
Male	[redacted]	27 (46.6)	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Mixed Ethnicity	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Weight for tisagenlecleucel manufacturing (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]
Karnofsky/Lanksy performance status, n (%)			
100	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]
60		[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]
<50		[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Disease history and prior therapies			
Diagnosis of disease, n (%)			
B-cell ALL	[redacted]	[redacted]	[redacted]
T-cell ALL	[redacted]	[redacted]	[redacted]
Age at initial diagnosis (years)			

Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]
Prior haematopoietic stem cell transplant (SCT)			
0	[redacted]	32 (55.2)	[redacted]
1	[redacted]	24 (41.4)	[redacted]
2	[redacted]	2 (3.4)	[redacted]
Disease status, n (%)			
Primary refractory	[redacted]	5 (8.6)	[redacted]
Chemo-refractory	[redacted]	53 (91.4)	[redacted]
Relapsed disease			
Number of previous lines of therapy, n (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	3.0	[redacted]
Min-Max	[redacted]	1–9	[redacted]
Time since initial diagnosis to first relapse (months)* †			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]
Time since initial diagnosis to first relapse category (months), n (%)†			
<18	[redacted]	[redacted]	[redacted]
18 to 36	[redacted]	[redacted]	[redacted]
>36	[redacted]	[redacted]	[redacted]
Time since most recent relapse to tisagenlecleucel infusion (months)* †			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]

[a] Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b] Data not available for all patients, hence why n numbers are less than the total full analysis set.
[c] This value for B2101J is for patients receiving >1 prior allo-SCT, rather than exactly two.
[d] Calculated for relapsed patients only
Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system; MRD: minimal residual disease; N/A: not applicable; NR: not reported; allo-SCT: stem cell transplantation; SD: standard deviation.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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 7. 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 8.

Table 7: 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.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017);[49] B2101J CSR supplementary appendix (30th Jan 2017).[62]

Table 8: Trial populations used for the analysis of outcomes of relevant clinical trials

Analysis set, n (%)	ELIANA	ENSIGN	B2101J[a]
Screened set	[redacted]	85 (100)	-
Enrolled set	[redacted]	73 (85.9)	[redacted]
Full analysis set[b]	[redacted]	58 (68.2)	[redacted]
Efficacy analysis set[c]	[redacted]	42 (49.4)	-
Safety set	[redacted]	58 (68.2)	[redacted]

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
[b]The FAS for ORR and DOR in ELIANA includes [redacted] patients to allow for at least 3 months between infusion and the data cut-off (31st Dec 2017). [c]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; NR: not reported.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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 9.

Table 9: 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 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
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).[34] 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 • 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 ORR of 30% (=23/76) would be	• 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).[34] 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 • 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 O'Brien-Fleming type boundary at one-	B2101J is a phase I/IIa study and the dropout rate was anticipated to be approximately 20%. 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)

	needed to claim success • Within the expected sample size of 76 patients 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%. • The actual number of patients to be enrolled would depend 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	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 • 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 • The actual number of patients enrolled depends 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	
Data management, patient withdrawals	• Patients in the study with unknown clinical response were considered non-responders • 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 • Other missing data were noted as missing where applicable	• Patients in the study with unknown clinical response were considered non-responders • 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 • Other missing data were noted as missing where applicable	• Patients in the study with unknown clinical response were considered non-responders • Other missing data were noted as missing where applicable

Abbreviations: CR: complete remission; CRi: complete remission with incomplete blood count recovery, IRC: Independent Review Committee; ORR: overall remission rate.
Source: ELIANA CSR (31st Dec 2017);[47] Maude *et al.* (2018) trial protocol;[63] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessments of ELIANA, ENSIGN and B2101J is presented below. These quality assessments were performed based on the 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.[64]

Table 10: 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 analysis? Appropriate methods to take these variables into account may include restriction, stratification, interaction terms, multivariate analysis, propensity	No	No	No

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: N/A: not applicable.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

B.2.6 Clinical effectiveness results of the relevant trials

Summary of the clinical effectiveness results of the relevant trials

ELIANA

- The study met its primary objective at the first interim analysis (data cut-off date: 17th Aug 2016), with an ORR of [redacted] (95% CI: [redacted]) within 3 months of tisagenlecleucel infusion.[47]
- As of the latest data cut-off (31st Dec 2017), the ORR remained consistent with the interim analysis; of the [redacted] patients in the efficacy analysis set, the ORR within 3 months of tisagenlecleucel infusion was [redacted] (95% CI: [redacted]). and [redacted] patients ([redacted], 95% CI: [redacted], [redacted]) achieved BOR of CR or CRi with bone marrow MRD negative disease (i.e. MRD <0.01%) demonstrating the depth and quality of the remissions achieved.[47]
- Median DoR has [redacted], with six-month DoR of [redacted] (95% CI: [redacted]). Median EFS and OS were also not reached, with six-month EFS of [redacted] (95% CI: [redacted]) and 12-month OS of [redacted] (95% CI: [redacted]).[47] These results support the durability of remission for the majority of patients and are comparable to the results from both ENSIGN and B2101J.[48, 49]
- Patient reported quality of life assessments [redacted] at three and six months post-tisagenlecleucel infusion compared to baseline, further supporting the benefit of treatment with tisagenlecleucel.[50]

ENSIGN

- The study met its primary objective at the first interim analysis (data cut-off 1st Feb 2016), with an ORR of 69.0% (95% CI: 52.9, 82.4) within 6 months of tisagenlecleucel infusion.[65]
- As of the latest data cut-off (6th Oct 2017), the ORR remained consistent with the interim analysis; of the 42 patients in the efficacy analysis set, the ORR within 6 months of tisagenlecleucel infusion was 69.0% (95% CI: 52.9, 82.4) and 27 patients (64.3%, 95% CI: 48.0, 78.4) achieved BOR of CR or CRi with bone marrow MRD negative disease.[48]

- Median DoR was not reached, with 6-month DoR of 71.4%. Median EFS was [redacted] months, with six-month EFS of [redacted]. 12-month OS was 62.6%.[48]

B2101J

- The efficacy data from B2101J are consistent with that seen in ELIANA and ENSIGN. As of the data cut-off date of 30th Jan 2017, the ORR at Day 28 was [redacted] ([redacted] patients).[49] Of the [redacted] patients who achieved a CR or CRi, [redacted] patients ([redacted], 95% CI: [redacted], [redacted]) had bone marrow MRD negative disease within 28 days of tisagenlecleucel infusion.[49]
- Median DoR was [redacted] months (95% CI: [redacted], NE) and in patients who had a BOR of CR or CRi, median EFS was [redacted] months (95% CI: [redacted], NE).[49] Median OS was [redacted] months, and the estimated probability of being alive was [redacted] at Month 12 and [redacted] at two years.[49]
- With the longest follow-up of [redacted] months (median [redacted] months), B2101J demonstrates the sustained duration of remission possible with tisagenlecleucel [49]

Pooled analysis

- A pooled analysis of all three tisagenlecleucel clinical trials was also conducted. The individual patient-level data (IPD) from each of the latest data cut-offs for all three clinical trials ELIANA ([redacted]), ENSIGN (n=58) and B2101J ([redacted]) were combined directly without adjustment to derive a pooled estimate of EFS and OS for tisagenlecleucel.
- In the pooled analysis, the probability of being event-free was [redacted] (95% CI: [redacted]) at one year, [redacted] (95% CI: [redacted]) at two years and [redacted] at (95% CI: [redacted]) at three years.[47]
- In terms of OS, the probability of survival at one year was [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]) at two years and [redacted] (95% CI: [redacted]) at three years, indicating durable remission and a high probability of survival up to 3 years after infusion.[47]

B.2.6.1 Clinical effectiveness results overview

An overview of the clinical effectiveness results from all three trials is provided in Table 11 below.

Table 11: Summary of the clinical effectiveness results in ELIANA, ENSIGN and B2101J

n (%)	ELIANA (N=[redacted]) (N=[redacted] for ORR and DoR)[a]	ENSIGN (N=58) (N=42 for ORR and DoR)[a]	B2101J (N=[redacted])[b]
Primary efficacy results			
BOR[c]			
ORR (CR+CRi) (95% CI; p value)	[redacted]	29 (69.0) (52.9, 82.4; <0.0001*)	[redacted]
CR	[redacted]	27 (64.3)	[redacted]
CRi	[redacted]	2 (4.8)	[redacted]
NR	[redacted]	9 (21.4)	[redacted]
Unknown[d]	[redacted]	4 (9.5)	[redacted]
ORR with bone marrow MRD negative (i.e. MRD <0.01%) (95% CI)	[redacted]	27 (64.3) (48.0, 78.4)	[redacted]

Secondary efficacy results			
DoR (/RFS)			
% event free at 6 months (95% CI)	[redacted]	71.4 (48.5, 85.5)	[redacted]
% event free at 12 months (95% CI)	[redacted]	61.2 (37.8, 78.0)	[redacted]
Median (months) (95% CI)	[redacted]	NE (5.9, NE)	[redacted]
EFS			
% event free at 6 months (95% CI)	[redacted]	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]	[redacted]
OS			
% at 6 months (95% CI)	[redacted]	79.3 (64.9, 88.4)	[redacted]
% at 12 months (95% CI)	[redacted]	62.6 (45.8, 75.6)	[redacted]
Median (months) (95% CI)	[redacted]	23.8 (8.8, NE)	[redacted]

[a]ORR and DoR from the latest data cut of ELIANA were assessed in patients with 3 months post-tisagenlecleucel infusion only. In ENSIGN these outcomes were assessed in patients with 6 months post-tisagenlecleucel infusion only (efficacy analysis set). [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: non-responder/no remission; ORR: overall remission rate
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

B.2.6.2 ELIANA

Data from the ELIANA trial are presented from the latest data cut-off date of 31st Dec 2017. All outcomes are presented for the full analysis set (all patients who received infusion of tisagenlecleucel; [redacted]), with the exception of ORR and DoR/RFS which were analysed in the efficacy analysis set (all patients treated with tisagenlecleucel at least 3 months prior to the data cut-off; [redacted]).

Primary outcome: ORR

ELIANA met its primary endpoint with an ORR of [redacted] (95% CI: [redacted]

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 null 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.[50]

An interim analysis was performed on the first 50 patients infused with tisagenlecleucel (data cut-off date: 17th Aug 2016). The primary endpoint was met and the ORR by IRC assessment during the 3 months post-tisagenlecleucel infusion in the full analysis set (all patients who received infusion of tisagenlecleucel) was 82.0% (41/50) (95% CI: 68.6, 91.4), with [redacted] patients ([redacted]) achieving a CR and [redacted] patients ([redacted]) achieving a CRi.[50]

As of the data cut-off date of 31st Dec 2017, the ORR in the full analysis set was [redacted] (95% CI: [redacted]). CR was achieved in [redacted] patients [redacted] and [redacted] patients [redacted] achieved a CRi.[47] Full results of the ORR analyses in the full analysis set are summarised in Table 12.

Table 12: Summary of IRC-assessed ORR within three months post-tisagenlecleucel infusion in ELIANA (full analysis set)

	Interim analysis: 17th August 2016 (full analysis set) (N=50)	Latest data cut-off: 31st Dec 2017 (full analysis set) (N=77)[a]
BOR, n (%)		
CR	[redacted]	[redacted]
CRi	[redacted]	[redacted]
NR/unknown[a]	[redacted]	[redacted]
ORR (CR + CRi), n (%) (95% CI; p value)	41 (82.0) (68.6, 91.4; <0.0001)	[redacted]

[a]ORR from the latest data cut of ELIANA (31st Dec 2017) was assessed in patients with 3 months post-tisagenlecleucel infusion only. [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; ORR: overall remission rate.
Source: Maude *et al.* (2018);[54] ELIANA CSR (31st Dec 2017).[47]

Bone marrow MRD status

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

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.[66] An MRD of less than 0.01% was defined as 'MRD negative disease'.[63]

As of the latest data cut-off date of 31st Dec 2017, [redacted] of the [redacted] patients infused with tisagenlecleucel ([redacted]) achieved an ORR of CR or CRi during the three months post-tisagenlecleucel infusion, of which [redacted] ([redacted]) of patients were bone marrow MRD negative (i.e. MRD <0.01%).[47] Similar results were also achieved at the interim analysis performed on the first 50 patients infused with tisagenlecleucel (data cut-off date: 17th Aug 2016), and in the results of the data cut-off of 25th Apr 2017.[50, 54]

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.[47] Full results of the bone marrow MRD status analyses are summarised in Table 13.

Table 13: Summary of IRC-assessed bone marrow MRD status within three months post-tisagenlecleucel infusion in ELIANA (full analysis set)

	Interim analysis: 17th August 2016 (full analysis set) (N=50)		Latest data cut-off: 31st Dec 2017 (full analysis set) (N=77)[a]	
	n (%)	95% CI	n (%)	95% CI
Achieved BOR of CR or CRi within 3 months of tisagenlecleucel infusion	[redacted]	[redacted]	[redacted]	[redacted]
With bone marrow MRD negative status (i.e. MRD% <0.01%), n (%) (CI; p-value)	[redacted]	[redacted]	[redacted]	[redacted]

[a]ORR from the latest 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; MRD: minimal residual disease.
Source: ELIANA CSR (31st Dec 2017).[47]

DoR

Remissions were durable; as of the latest data cut-off median DoR and RFS had not been reached

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 (31st Dec 2017), 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.[50]

As of the latest data cut-off date (31st Dec 2017), [redacted] of patients who had achieved a BOR of CR or CRi had not relapsed and median DoR had not been reached (95% CI: [redacted]).[47] The estimated rate of RFS after onset of remission was [redacted] (95% CI: [redacted]) at Month 6 and [redacted] (95% CI: [redacted]) at Month 12.[47] The Kaplan-Meier plot for the analysis of DoR (data cut-off date of 31st Dec 2017) is presented in Figure 10.

Figure 10: Kaplan-Meier plot for IRC-assessed DoR (censoring for allo-SCT) in ELIANA (full analysis set)[a]

[a]As of data cut-off 31st Dec 2017.
Abbreviations: CI: confidence interval; DoR: duration of response; NE: not estimable.
Source: ELIANA CSR (31st Dec 2017).[47]

EFS

Median EFS had not been reached at the time of the latest data cut-off

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.[63]

At the time of the latest data cut-off (31st Dec 2017), median EFS had not yet been reached (95% CI:) and only of the patients infused with tisagenlecleucel () had experienced an EFS event (death due to any cause after remission, relapse, or treatment failure). The probability of being event-free was (95% CI:) at Month 6 and at Month 12 (95% CI:).[47] The Kaplan-Meier plot for the analysis of EFS at the data cut-off date of 31st Dec 2017 is presented in Figure 11.

Figure 11: Kaplan-Meier plot for IRC-assessed EFS (censoring for allo-SCT) in ELIANA (full analysis set)[a]

[a]As of data cut-off 31st Dec 2017.
Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: ELIANA CSR (31st Dec 2017).[47]

OS

OS data demonstrate durable remissions and a high probability of long-term survival

OS was defined as the time from first tisagenlecleucel infusion to the date of death due to any cause.[63] As of the latest data cut-off of 31st Dec 2017, median OS had not yet been reached and only [redacted] patients ([redacted]) had died following tisagenlecleucel infusion. The probability of survival at Month 6 was [redacted] (95% CI: [redacted]), and at Month 12 was [redacted] (95% CI: [redacted]), indicating durable remission and a high probability of survival up to 12 months after infusion.[47] The Kaplan-Meier plot for the analysis of OS at the data cut-off date of 31st Dec 2017 is presented in Figure 12.

Figure 12: Kaplan-Meier plot for OS in ELIANA (full analysis set)[a]

[a]As of data cut-off 31st Dec 2017.
Abbreviations: CI: confidence interval; OS: overall survival; NE: not estimable.
Source: ELIANA CSR (31st Dec 2017).[47]

Patient-reported outcomes

Patient-reported outcomes (PROs) were assessed via the paediatric quality of life questionnaire (PedsQL) and the EQ-5D-3L questionnaire in patients ≥8 years old only.[67, 68]

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.[69] 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, 18 and 24 compared to Baseline, indicating consistent improvement of HRQoL up to two years 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 13).[47]

In the full analysis set (data cut-off 31st Dec 2017), the mean change from Baseline in the PedsQL total score was [redacted] at Month 6, [redacted] at Month 12, [redacted] at Month 18 and [redacted] at Month 24, indicating an overall improvement in HRQoL after tisagenlecleucel infusion.[47] The minimal clinically important difference for the PedsQL total scores has been estimated using distribution-based methods to be 4.4 for self-report.[70] Thus, the observed changes from Baseline in the PedsQL total score and in each PedsQL subscale at each time point appear to 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 [redacted] at Month 6, [redacted] at Month 12, [redacted] at Month 18, and [redacted] at Month 24, again indicating an overall improvement in HRQoL following tisagenlecleucel infusion (see Figure 13).[47] The number of patients are 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 FACT-G (Pickard *et al.* [2007]), the observed changes from Baseline in EQ VAS at each timepoint appear to represent meaningful improvements in HRQoL.[71] Additionally, while the mean EQ VAS score at Baseline [redacted] was comparable to that of patients sampled from cancers of various aetiologies (Pickard *et al*. [2007]), the mean scores at Month 6 ([redacted]), Month 12 ([redacted]), Month 18 ([redacted]), and Month 24 ([redacted]) were comparable to normative means of general populations.[47, 71, 72]

Figure 13: Summary of PedsQL and EQ VAS scores in ELIANA (patients ≥8 years old achieving CR/CRi)

Mean change from baseline in patients who had both baseline and post-baseline score. Only patients 8 years or older were required to complete the assessments.
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);[70] [b]Pickard *et al.* (2007);[71] [c]Varni *et al.* (2001);[73] [d]Janssen *et al.* (2014).[72]

B.2.6.3 ENSIGN

Data from the ENSIGN trial are presented from the latest data cut-off date of 6th Oct 2017, which provides median follow-up of [redacted] months and a maximum follow-up of [redacted] months.[48] All outcomes are presented for the full analysis set (all patients who received infusion of tisagenlecleucel; n=58) with the exception of ORR and DoR/RFS which were analysed in the efficacy analysis set (all patients treated with tisagenlecleucel at least 6 months prior to the data cut-off; n=42).

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.[48]

As of the latest data cut-off date of 6th Oct 2017, the study met its primary endpoint with an ORR of 69.0% (29/42) (95% CI: 52.9, 82.4). CR was achieved in 27 patients (64.3%) and two patients (4.8%) achieved a CRi.[48] In sensitivity analyses performed using local Investigator assessment, there was [redacted] concordance between IRC assessment and local Investigator assessment of ORR.[48] Full results of the ORR analysis are summarised in Table 14.

Table 14: Summary of IRC-assessed ORR within six months post-tisagenlecleucel infusion in ENSIGN (efficacy analysis set)

	ENSIGN (efficacy analysis set) (N=42)
BOR, n (%)	
CR	27 (64.3)
CRi	2 (4.8)
No response	9 (21.4)
Unknown[a]	4 (9.5)
ORR (CR + CRi), n (%)(95% CI; p value)[b]	29 (69.0) (52.9, 82.4; <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; ORR: overall remission rate.
Source: ENSIGN CSR (6th Oct 2017).[48]

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'.[48]

As of the latest data cut-off date of 6th Oct 2017, 29/42 patients (69.0%; 95% CI: 52.9, 82.4) achieved an ORR of CR or CRi during the six months post-tisagenlecleucel infusion, of which 27 patients (64.3%; 95% CI: 48.0, 78.4) were bone marrow MRD negative (i.e. MRD <0.01%) and therefore achieved bone marrow MRD negative remission.[48] Full results of the bone marrow MRD status analysis within six months post-tisagenlecleucel infusion are summarised in Table 15.

Table 15: Summary of IRC-assessed bone marrow MRD status within six months post-tisagenlecleucel infusion in ENSIGN (efficacy analysis set)

	ENSIGN (efficacy analysis set) (N=42)	
	n (%)	95% CI
Achieved BOR of CR or CRi within 6 months	29 (69.0)	52.9, 82.4

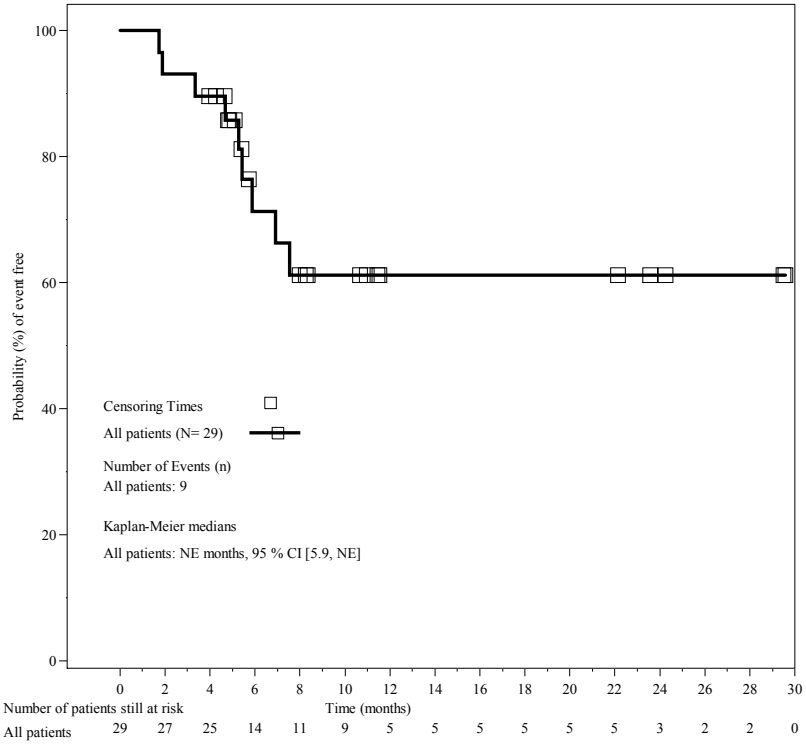
With bone marrow MRD negative status (i.e. MRD% <0.01%)	27 (64.3)	48.0, 78.4

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; MRD: minimal residual disease.
Source: ENSIGN CSR (6th Oct 2017).[48]

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 data (6th Oct 2017), 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.[48] 20/29 patients (69.0%) who achieved a BOR of CR or CRi had not relapsed, and median DoR had not been reached. The estimated rate of RFS after onset of remission was 71.4% (95% CI: 48.5, 85.5) at Month 6 and 61.2% (95% CI: 37.8, 78.0) at Month 12. A pre-planned sensitivity analysis of DoR without censoring at time of allo-SCT was conducted and the results were similar to the main analysis (full results not shown).[48] The Kaplan-Meier plot for the analysis of DoR at the data cut-off date of 6th Oct 2017 is presented in Figure 14.

Figure 14: Kaplan-Meier plot for IRC-assessed DoR (censoring for allo-SCT) in ENSIGN (efficacy analysis set)[a]



[a]As of data cut-off 6th Oct 2017. Only patients who achieved CR or CRi are included. Time is relative to onset of remission, 1 month = 30.4375 days.
Abbreviations: CI: confidence interval; DoR: duration of response; NE: not estimable.
Source: ENSIGN CSR (6th Oct 2017).[48]

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.[48]

At the time of the latest data cut-off (6th Oct 2017), median EFS was [redacted] months (95% CI: [redacted]) and [redacted] of the [redacted] patients ([redacted]) reported treatment failure or relapse, as determined by IRC assessment.[48] The estimated probability of being event-free was [redacted] (95% CI: [redacted]) at Month 6 and [redacted]% (95% CI: [redacted] at Month 12.[48] The Kaplan-Meier plot for the analysis of EFS at the data cut-off date of 6th Oct 2017 is presented in Figure 15.

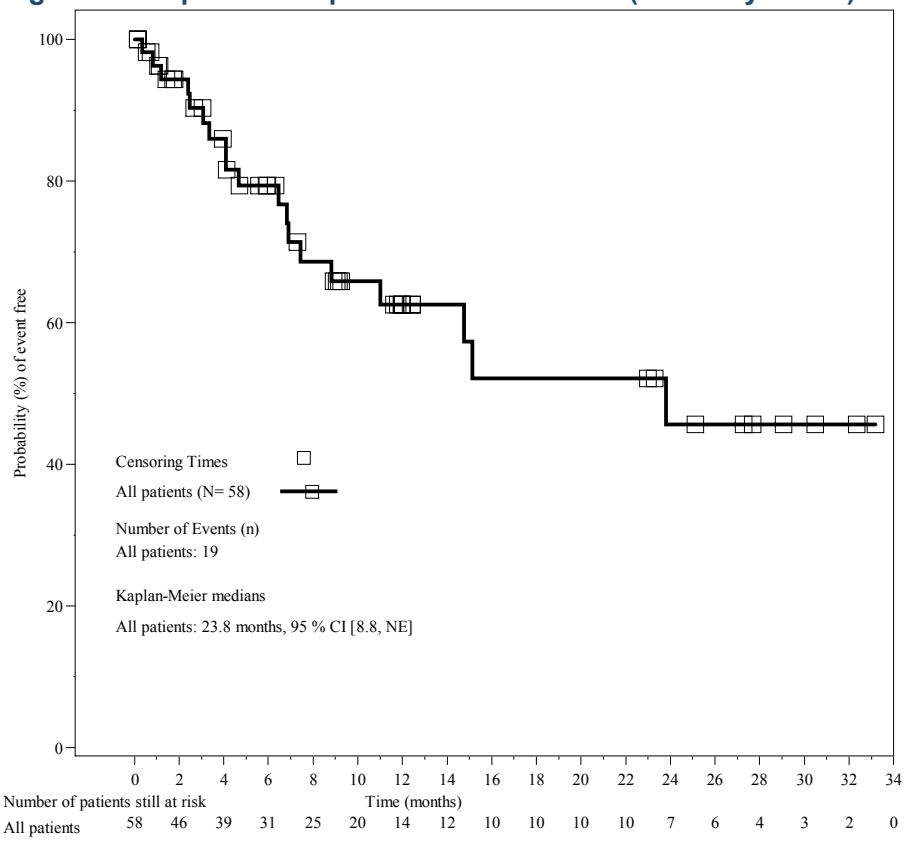
Figure 15: Kaplan-Meier plot for EFS (censoring for allo-SCT) in ENSIGN (full analysis set)[a]

[a]As of data cut-off 6th Oct 2017. 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 (6th Oct 2017).[48]

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 6th Oct 2017, median OS was 23.8 months (95% CI: 8.8, NE) and 19/58 patients (32.8%) had died following tisagenlecleucel infusion; however, median OS should be interpreted with caution because only seven patients were at risk beyond that point. The probability of survival at Month 6 was 79.3% (95% CI: 64.9, 88.4), and at Month 12 was 62.6% (95% CI: 45.8, 75.6).[48] The Kaplan-Meier plot for the analysis of OS at the data cut-off date of 6th Oct 2017 is presented in Figure 16.

Figure 16: Kaplan-Meier plot for OS in ENSIGN (full analysis set)[a]



[a]As of data cut-off 6th Oct 2017. 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 (6th Oct 2017).[48]

B.2.6.4 B2101J

Data from the B2101J trial are presented from the latest data cut-off date of 30th Jan 2017, which provides a median follow-up of [redacted] months and a maximum follow-up of [redacted] months.[49] All outcomes are presented for the full analysis set (all patients who received infusion of tisagenlecleucel) in the [redacted] 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.[49]

As of the latest data cut-off date of 30th Jan 2017, the ORR was [redacted] (95% CI: [redacted]), with [redacted] patients ([redacted]) achieving a CR and [redacted] patients ([redacted]) achieving CRi by Day 28 post-tisagenlecleucel infusion. In the analysis of BOR at any time, ORR was [redacted] (95% CI: [redacted]), with [redacted] patients ([redacted]) achieving CR and [redacted] patients ([redacted]) with CRi. Only [redacted] patients ([redacted]) did not respond to treatment with tisagenlecleucel.[49] Full results of the ORR analysis are summarised in Table 16.

Table 16: Summary of ORR at Day 28 in B2101J

	B2101J (full analysis set) (N=56)[a]
	n (%) (95% CI)
Overall response at Day 28	
CR	[redacted]
CRi	[redacted]
No response	[redacted]
Unknown	[redacted]
ORR: CR + CRi	[redacted]
BOR at any time	
CR	[redacted]
CRi	[redacted]
No response	[redacted]
Unknown	[redacted]
ORR: CR + CRi (at any time)	[redacted]

[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 (30th Jan 2017).[49]

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'.[49]

As of the latest data cut-off of 30th Jan 2017, [redacted] of the [redacted] patients infused with tisagenlecleucel ([redacted]; 95% CI: [redacted]) 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 [redacted] patients ([redacted]), and at any time following infusion, [redacted] patients achieved bone marrow MRD negative remission.[49] Full results for the analysis of remission with MRD negative bone marrow are summarised in Table 17.

Table 17: Summary of bone marrow MRD status in B2101J (full analysis set)

	B2101J (full analysis set) (N=56)[a]	
	n (%)	95% CI
Achieved CR/CRi within 28 days	[redacted]	[redacted]
With MRD negative disease status (i.e. MRD%<0.01%)	[redacted]	[redacted]
Achieved CR/CRi at any time	[redacted]	[redacted]
With MRD negative disease status (i.e. MRD%<0.01%)	[redacted]	[redacted]

[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: B2110J CSR (30th Jan 2017).[49]

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 (30th Jan 2017), 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.[49]

As of the latest data cut-off date (30th Jan 2017), [redacted] ([redacted]) of patients who achieved a BOR of CR or CRi had not suffered an event (relapse or death due to underlying cancer), with median DoR of [redacted] months. The estimated relapse-free rate after onset of remission was [redacted] (95% CI: [redacted]) at Month 12, [redacted] (95% CI: [redacted]) at Month 24, and [redacted] (95% CI: [redacted]) at Month 36.[49] The Kaplan-Meier plot for the analysis of DoR at the data cut-off date of 30th Jan 2017 is presented in Figure 17.

Figure 17: Kaplan-Meier plot for DoR in B2101J (full analysis set)[a]

[a]As of data cut-off 30th Jan 2017.
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 (30th Jan 2017).[49]

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.[49]

As of the latest data cut-off date (30th Jan 2017), median EFS was [redacted] months (95% CI: [redacted]), and [redacted] patients ([redacted]) had experienced an event. The estimated probability of being event-free was [redacted] (95% CI: [redacted]) at Month 12, [redacted] (95% CI: [redacted]) at Month 24, and [redacted] (95% CI: [redacted]) at Month 36.[49]

The Kaplan-Meier plot for the analysis of EFS at the data cut-off date of 30th Jan 2017 is presented in Figure 18.

Figure 18: Kaplan-Meier plot for EFS in B2101J (full analysis set)[a]

[a]As of data cut-off 30th Jan 2017.
Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: B2101J CSR (30th Jan 2017).[49]

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 30th Jan 2017, median OS was [redacted] months (95% CI: [redacted]) and [redacted] patients ([redacted]) had died following tisagenlecleucel infusion. The probability of survival was [redacted] (95% CI: [redacted]) at Month 12, [redacted] (95% CI: [redacted]) at Month 24, and [redacted] (95% CI: [redacted]) at Month 36, demonstrating durable remission and a high probability of survival up to three years post-tisagenlecleucel infusion.[49] The Kaplan-Meier plot for the analysis of OS at the data cut-off date of 30th Jan 2017 is presented in Figure 19.

Figure 19: Kaplan-Meier plot for OS in B2101J (full analysis set)[a]

[a]As of data cut-off 30th Jan 2017.
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 (30th Jan 2017).[49]

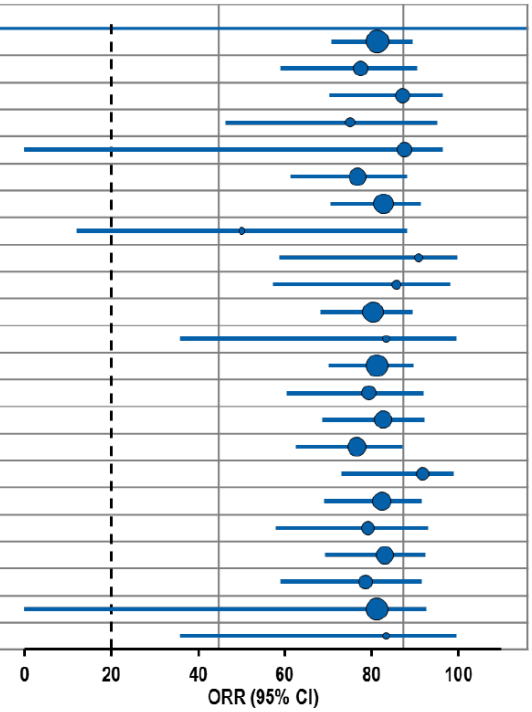
B.2.7 Subgroup analysis

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, data cut-off 25th Apr 2017 (subgroup analyses are not yet available for the latest data cut-off of 31st Dec 2017), subgroup ORR analyses were conducted for subgroups with at least 5 patients. The ORR by IRC assessment was consistently ≥20% across all subgroups evaluated (hence the null hypothesis that the ORR was ≤20% could be rejected; see Figure 20). In the ENSIGN trial (data cut-off 6th Oct 2017), the ORR by IRC assessment across the various subgroups with at least five patients was consistently ≥55% (ranging from 55.6% to 93.3%) and in B2101J (data cut-off 30th Jan 2017), the ORR by IRC assessment at Day 28 was similarly high in all pre-specified subgroups analysed (≥80% in all subgroups). Forest plots for the subgroup analyses from ENSIGN and B2101J are presented in Appendix E.

Figure 20: ORR within 3 months post-tisagenlecleucel infusion by IRC assessment. Forest plot for subgroups from ELIANA (full analysis set)

		n
Overall		75
Age, years	<10	31
	≥10-17	31
	≥18	13
Sex	Female	32
	Male	43
Race	White	58
	Asian	6
	Other	11
Ethnicity	Hispanic or Latino	14
	Other	61
Response status at study entry	Primary refractory	6
	Relapsed disease	69
Prior alloHSCT	No	29
	Yes	46
Enrollment bone marrow tumor burden*	High	51
	Low	24
Complex karyotypes†	No	51
	Yes	24
Any high-risk mutations‡	No	47
	Yes	28
Down syndrome	No	69
	Yes	6



*Low disease burden, <50% lymphoblasts in bone marrow; high disease burden, ≥50% lymphoblasts in bone marrow. † ≥5 unrelated abnormalities. ‡ BCR-ABL1, MLL rearrangement, hypoploidy, lesions associated with BCR-ABL1–like gene signature, or complex karyotype.
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.
Abbreviations: CI: confidence interval; IRC: independent review committee; ORR: overall remission rate; allo-SCT: stem cell transplantation.
Source: Maude *et al.* (2018) supplementary appendix.[31]

B.2.8 Meta-analysis

For the purposes of increasing the overall available sample size for tisagenlecleucel and allowing the use of the longest-term follow-up data available within the economic analysis, 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. 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 5).

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). 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 ([redacted], [redacted] and [redacted] in ELIANA, ENSIGN, and B2101J, respectively) and the age range across all three trials was between 1 and 25.[47-49]

Key patient baseline characteristics can be found in Table 18 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.[74] 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 18: Key patient baseline characteristics from the pooled analysis

	ELIANA (N=[redacted])	ENSIGN (N=58)	B2101J (N=[redacted])[a]	Pooled analysis
Sex, n (%)				
Female	[redacted]	31 (53.4)	[redacted]	[redacted]
Male	[redacted]	27 (46.6)	[redacted]	[redacted]
Age				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	12	[redacted]	[redacted]
Min	[redacted]	3	[redacted]	[redacted]
Max	[redacted]	25	[redacted]	[redacted]
Weight				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]

Max	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black	-	-	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Pacific Islander	-	-	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Mixed Ethnicity	-	-	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Karnofsky/Lanksy performance status, n (%)				
100	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	-	[redacted]
50	[redacted]	[redacted]	-	[redacted]
<50	[redacted]	[redacted]	-	[redacted]
Missing	-	-	[redacted]	[redacted]
Diagnosis of disease, n (%)				
B-cell ALL	[redacted]	[redacted]	[redacted]	[redacted]
T-cell ALL	-	-	[redacted]	[redacted]
Prior haematopoietic stem cell transplant (SCT)				
0	[redacted]	32 (55.2)	[redacted]	[redacted]
1	[redacted]	24 (41.4)	[redacted]	[redacted]
2	[redacted]	2 (3.4)	[redacted]	[redacted]
Disease status, n (%)				
Primary refractory	[redacted]	5 (8.6)	[redacted]	[redacted]
Chemo-refractory/relapsed disease	[redacted]	53 (91.4)	[redacted]	[redacted]

[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: SD: standard deviation.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

The individual patient-level data (IPD) from each of the latest data cut-offs for all three clinical trials ELIANA ([redacted]), ENSIGN (n=58) and B2101J ([redacted]) were combined directly without adjustment to derive a pooled estimate of EFS and OS for tisagenlecleucel. A total of [redacted] patients were therefore included in the pooled analysis.

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.[63]

In the pooled analysis, median EFS is 28.9 months (95% CI: [redacted]) and [redacted] of the [redacted] patients infused with tisagenlecleucel ([redacted]) had experienced an EFS event (death due to any cause after remission, relapse, or treatment failure). The probability of being event-free was [redacted] (95% CI: [redacted]) at one year, [redacted] (95% CI: [redacted]) at two years and [redacted] at (95% CI: [redacted]) at three years.[47]

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

Figure 21: Kaplan-Meier curves for EFS in ELIANA, ENSIGN and B2101J and the pooled analysis

Abbreviations: EFS: event-free survival.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

OS

OS was defined as the time from first tisagenlecleucel infusion to the date of death due to any cause.[63] In the pooled analysis, median OS is [redacted] months (95% CI: [redacted]) and [redacted] patients ([redacted]) had died following tisagenlecleucel infusion. The probability of survival at one year was [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]) at two years and [redacted] (95% CI: [redacted]) at three years, indicating durable remission and a high probability of survival up to 3 years after infusion.[47]

The Kaplan-Meier plot showing the OS curve for each trial separately, together with the pooled OS curve is presented in Figure 22 below.

Figure 22: OS Kaplan-Meier curves for ELIANA, ENSIGN and B2101J and the pooled analysis

Abbreviations: OS: overall survival.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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 (FLA-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 66 studies ultimately identified in the SLR, two trials were identified that investigated the use of blinatumomab in paediatric patients aged up to 18 years with r/r B-cell ALL: a phase II clinical trial (n=70) published by von Stackelberg *et al.* (2016) and an expanded open-access study (n=40) published as a poster at the American Society of Clinical Oncology conference 2017 (the RIALTO study).[35, 75] 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 was not considered further 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. 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 larger of the two identified clinical trials for blinatumomab, the von Stackelberg *et al.* (2016) study alone was considered for further inclusion within an indirect treatment comparison. Further details of this study are presented in Appendix D. The use of the RIALTO study was explored within the economic analysis.

Salvage chemotherapy (FLA-IDA)

No trials were identified for FLA-IDA in paediatric patients with r/r B-cell ALL. As such, an assessment of the included studies was performed to identify efficacy data that could be used as a proxy for the efficacy of FLA-IDA.

The 66 included studies were first assessed 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.

Full details of the eligibility criteria for ELIANA, ENSIGN and B2101J can be found in Appendix L. Additional study population criteria were applied to the 66 studies included in the SLR to systematically select the studies with populations comparable to the tisagenlecleucel clinical trials. A total of 10 studies in first relapse patients only, first relapse/primary refractory patients only, or unclear populations were subsequently excluded. The second step was to review the remaining studies in terms of the availability of relevant EFS and OS measures reported in the form of Kaplan-Meier curves; of these, 8 studies without an OS Kaplan-Meier curve were excluded. As a last step, any studies conducted in Japan were also excluded from consideration, and they were not deemed to be conducted in patient populations similar enough to the UK. Finally, the studies of blinatumomab were not considered to represent the efficacy of FLA-IDA and were removed.

The remaining 6 trials are presented in Table 28. These were presented for review by UK clinical experts, who advised on whether the efficacy outcomes could be considered comparable to the outcomes expected with FLA-IDA. Feedback from UK clinical experts was that median OS with FLA-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 (Hijaya *et al.* [2011; Miano *et al.* [2012]; Cooper *et al.* [2013]) or clofarabine monotherapy (Jeha *et al.* [2006]). 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 FLA-IDA. 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 (FLA-IDA) comparator within this submission. The other clofarabine studies (Hijaya *et al.* [2011; Miano *et al.* [2012]) relate to combination therapy and were therefore excluded on this basis.

Table 19: Clinical evidence identified to be used as a proxy for the efficacy of FLA-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)	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)	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)	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 at study entry 12.5 (4–21)	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%) AIEOP ALL 95 (24%) DFCI ALL (12%)	~9 months (B-cell patients only)
Cooper *et al.* (2013)	Single-arm clinical trial	21 patients (8 given clofarabine at 40	US/ Canada	• Included patients 1–21 years • Age at initial	Clofarabine + cytarabine	• 2nd/3rd relapse or refractory to re-induction therapy in first	• Excluded ALL patients that received allo-SCT within 12	Relapsed patients allowed to have no more than 3	~3 months

		mg/m^2 and 13 at 52 mg/m^2)		diagnosis 6.2 (0.27–21.8) years • Age at study entry 11.8 (1.2–25.7)		relapse • 86% in 2nd **or** 3rd relapse • 14% refractory	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	prior induction regimens	
Messinger *et al.* (2012)	Single-arm clinical trial	22 patients	US	Age <21 at initial diagnosis >1 year at study entry Median age at study entry 12 (1.3–22.3)	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 • 77% failed 2 regimes • 23% failed 3 regimes	~9 months
Jeha *et al.* (2006)	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: EFS: event-free survival; NR: not reported; OS: overall survival; allo-SCT: stem-cell transplant.

Matched-adjusted indirect treatment comparison

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 in order to explore adjustments of the pooled tisagenlecleucel population to more closely match that of the von Stackelberg *et al.* (2016) and Jeha *et al.* (2006) population, respectively, and hence account for any impact of population differences on OS estimates.[34, 35] 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.

An overview of the MAIC results for OS are presented below. Full details of the methodology of this approach are presented in Appendix D. The OS benefit observed for tisagenlecleucel in the naïve comparison remained consistent and statistically significant at the 95% confidence level in the MAIC. The resulting HRs are presented in Table 20.

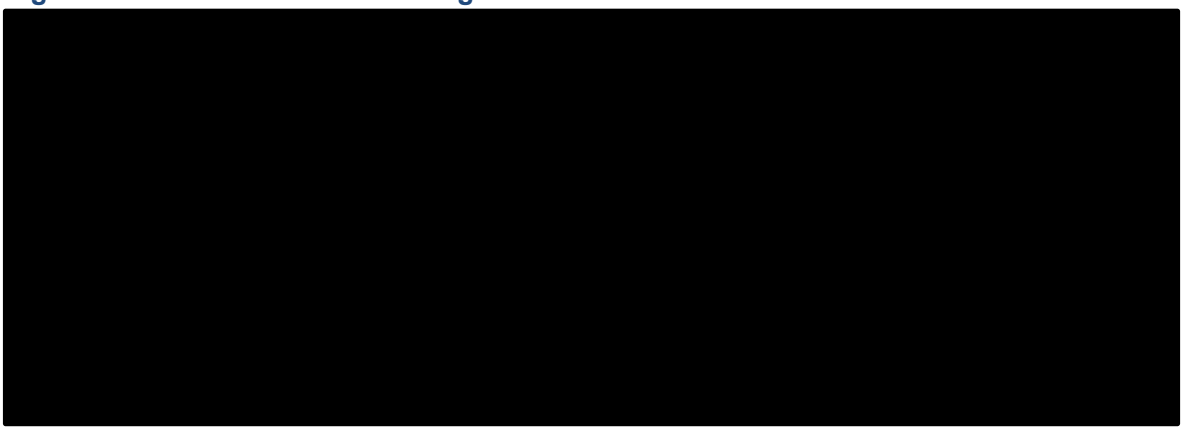
Table 20: Overall survival hazard ratios

Adjustment scenario	Naïve comparison		MAIC comparison	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Tisagenlecleucel vs blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Tisagenlecleucel vs salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison.
Source: ELIANA CSR (31st Dec 2017);[47]; ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017);[49] von Stackelberg *et al.* (2016)[35]; Jeha *et al.* (2006).[34]

The Kaplan-Meier plot of OS for the matched tisagenlecleucel cohort versus blinatumomab is presented in Figure 23 and for the matched tisagenlecleucel cohort versus salvage chemotherapy (using clofarabine monotherapy as a proxy for FLA-IDA) is presented in Figure 24. In the comparison to blinatumomab, the matched and unmatched curves were seen to be very similar, with the matched curve associated with a slightly higher plateau than the unmatched curve. In the comparison to salvage chemotherapy the matched curve was seen to be associated with slightly lower survival for earlier timepoints, but a higher plateau at the later timepoints than the unmatched curve. In both comparisons, the 95% confidence intervals of the matched and unmatched curves overlapped, indicating that differences between the unmatched and unmatched curves may reflect uncertainty inherent in the sample estimates rather than a true difference in efficacy.

Figure 23: Overall survival for tisagenlecleucel versus blinatumomab



Shaded regions represent 95% CIs.
Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: Blinatumomab: von Stackelberg *et al.* (2016);[35] tisagenlecleucel: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

Figure 24: Overall survival for tisagenlecleucel versus salvage chemotherapy

Shaded regions represent 95% CIs.
Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: Salvage chemotherapy (using clofarabine monotherapy as a proxy for FLA-IDA): Jeha *et al.* (2006); tisagenlecleucel: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

B.2.10 Adverse reactions

Summary of clinical trial safety analysis

- As of the latest data cuts reported in this submission, a total of [redacted] patients had received infusion with tisagenlecleucel and were analysed as part of the safety sets of ELIANA, ENSIGN and B2101J. Based on these safety analyses, the safety profile of tisagenlecleucel is well characterised and was consistent across all three clinical trials.[47-49]
- The most frequently occurring AE, regardless of study drug relationship, in all three trials was cytokine release syndrome (CRS), which was reported in [redacted]), 47 (81.0%) and [redacted] patients in the ELIANA, ENSIGN and B2101J trials, respectively.[47-49] CRS is an expected AE in patients infused with tisagenlecleucel, as a class-effect of T-cell directed therapies and an on-target mechanism of action effect. CRS is generally reversible, and can be effectively managed with treatment guidelines.[31]

- In the ELIANA trial, AEs were reported primarily within eight weeks post-tisagenlecleucel infusion and the incidence of all AEs decreased substantially after this time point. Of note, no patients had CRS after this eight-week period and only [redacted] had AEs more than one year post-tisagenlecleucel infusion.[50]
- In terms of SAEs, CRS was the most commonly reported SAE regardless of study drug relationship, occurring in [redacted], [redacted] and [redacted] patients in the ELIANA, ENSIGN and B2101J trials, respectively. Febrile neutropenia was consistently the next most common ([redacted], [redacted] and [redacted], respectively), followed by hypotension ([redacted], [redacted] and [redacted], respectively).[47-49]
- Across all three trials, a total of [redacted] deaths were reported post-tisagenlecleucel infusion. Deaths occurring within 30 days post-tisagenlecleucel infusion were reported for [redacted] patients ([redacted]) and [redacted] patients ([redacted]) in the ELIANA and ENSIGN trials respectively. None of these deaths were due to the tisagenlecleucel infusion.
- In B2101J, no deaths occurred within 30 days of the first tisagenlecleucel infusion and deaths were reported for [redacted] patients within 30 days of the last tisagenlecleucel infusion (patients in B2101J could receive more than one infusion). In the period more than 30 days post-tisagenlecleucel infusion, [redacted] and [redacted] patients died in the ELIANA and ENSIGN trials, respectively. In B2101J, [redacted] patients [redacted] died more than 30 days after the last tisagenlecleucel infusion.[47-49]

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, [redacted] patients ([redacted]) out of the [redacted] 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). Of the 79 patients that received tisagenlecleucel, [redacted] patients ([redacted]) received tisagenlecleucel doses within the protocol-specified target dose range. [redacted] patients ([redacted]) received a dose above the target range and [redacted] patients [redacted] received a dose below the target range. The median total tisagenlecleucel dose infused was [redacted] cells (range [redacted]) and the median weight-adjusted tisagenlecleucel dose infused was [redacted] cells/kg (range [redacted]).[47]

In ENSIGN, 58 patients (79.5%) out of the 73 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 58 patients that received tisagenlecleucel, 49 patients (84.5%) received tisagenlecleucel doses within the protocol-specified target dose range as specified above and nine patients (15.5%) received a below target dose range. The median total tisagenlecleucel dose infused was [redacted] cells (range [redacted]) and the median weight-adjusted tisagenlecleucel dose infused was 3.55×10^6 cells/kg (range 0.2×10^6 to 5.0×10^6).[48]

In the B2101J trial, [redacted] patients of the [redacted] 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 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.[49] The median total tisagenlecleucel dose infused during the overall study was [redacted] cells (range [redacted]) and the median weight-adjusted tisagenlecleucel dose infused during the overall study was [redacted] cells/kg (range [redacted]).[49]

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 21 below. Across all three trials, as of the latest data cuts reported in this submission, a total of [redacted], 58 and [redacted] patients had received infusion with tisagenlecleucel and were analysed in the safety sets of ELIANA, ENSIGN and B2101J, respectively.[47-49]

Table 21: Overall summary of AEs in ELIANA, ENSIGN and B2101J (safety set)

Adverse event, n (%)	ELIANA (safety set) (N=[redacted])	ENSIGN (safety set) (N=58)	B2101J (safety set) (N=[redacted])[a]
Number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Death within 30 days post-tisagenlecleucel infusion	[redacted]	[redacted]	[redacted]
Death >30 days post-tisagenlecleucel infusion	[redacted]	[redacted]	[redacted]
Patients with serious or other significant events			
Any time post-tisagenlecleucel infusion			
SAE	[redacted]	45 (77.6)	[redacted]
SAE suspected to be study drug-related	[redacted]	42 (72.4)	[redacted]
Grade 3/4 AE	[redacted]	50 (86.2)	[redacted]
Grade 3/4 AE suspected to be study drug-related	[redacted]	46 (79.3)	[redacted]
Within 8 weeks post-tisagenlecleucel infusion			
SAE	[redacted]	43 (74.1)	-
SAE suspected to be study drug-related	[redacted]	41 (70.7)	-

Grade 3/4 AE	[redacted]	48 (82.8)	-
Grade 3/4 AE suspected to be study drug-related	[redacted]	44 (75.9)	-
>8 weeks post-tisagenlecleucel infusion			
	(N=[redacted])	**(N=42)**	
SAE	[redacted]	17 (40.5)	-
SAE suspected to be study drug-related	[redacted]	6 (14.3)	-
Grade 3/4 AE	[redacted]	19 (45.2)	-
Grade 3/4 AE suspected to be study drug-related	[redacted]	11 (26.2)	-

[a]Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only.
*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). **Value calculated based on 22 deaths post-tisagenlecleucel infusion, and three of these occurring within 30 days of the last infusion. Therefore, 19 occurred 30 days after the last infusion (33.9% of 56).
All deaths during both study follow-up and survival follow-up are summarised.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: ELIANA CSR (31st Dec 2017),[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

Deaths

A total of [redacted] deaths ([redacted]) occurred in the ELIANA trial post-tisagenlecleucel infusion (data cut-off 31st Dec 2017). [redacted] patients died within 30 days post-tisagenlecleucel infusion; [redacted] due to cerebral haemorrhage and [redacted] due to underlying disease progression. The other 21 deaths occurred more than 30 days post-tisagenlecleucel infusion. Of these, [redacted] deaths ([redacted]) were attributed to underlying disease progression, [redacted] was due to viral encephalitis, [redacted] due to systematic mycosis, [redacted] due to lower respiratory tract infection, [redacted] due to hepatobiliary disease and [redacted] due to an unknown reason.[47]

A total of 19 deaths (32.8%) occurred in the ENSIGN trial post-tisagenlecleucel infusion (data cut-off 6th Oct 2017). [redacted] patients died within 30 days post-tisagenlecleucel infusion; [redacted] due to underlying disease progression and [redacted] due to embolic stroke. The other 17 deaths occurred more than 30 days post-tisagenlecleucel infusion. Of these, 15 were attributed to underlying disease progression, one due to acute respiratory failure and one due to complications of transplant surgery.[48]

A total of [redacted] deaths ([redacted]) occurred in the B2101J trial post-tisagenlecleucel infusion (data cut-off 30th Jan 2017). No deaths were reported within 30 days after the first tisagenlecleucel infusion, whereas [redacted] patients ([redacted]) died within 30 days after the final tisagenlecleucel infusion, and [redacted] patients [redacted]) died more than 30 days after the last tisagenlecleucel infusion.[49]

AEs post-tisagenlecleucel infusion, regardless of study drug relationship

AEs regardless of study drug relationship occurred in [redacted] patients in ELIANA and B2101J, and [redacted] patients in ENSIGN.[47-49] In the ELIANA trial, regardless of study drug relationship, the most frequent AEs overall were CRS, pyrexia, decreased appetite and hypogammaglobulinaemia, which occurred in at any grade in [redacted], [redacted], [redacted] and [redacted] patients, respectively.[47] CRS was also the most common AE regardless of study drug relationship in ENSIGN, followed by hypogammaglobulinaemia, a decreased white blood cell count and anaemia. These AEs occurred in 81.0%, [redacted], [redacted] and [redacted] patients, respectively.[48] Lastly, in B2101J, decreased white

blood cell count was the most common AE regardless of study drug relationship, occurring in [redacted] patients. The next most common AEs were a decrease in haemoglobin, a decreased neutrophil count and CRS, occurring in [redacted], [redacted] and [redacted] patient, respectively.[49]

A summary of frequently reported AEs post-tisagenlecleucel infusion, regardless of study drug relationship for all three trials is presented in Table 22.

Table 22: 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=58)			B2101J (safety set) (N=56)[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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	47 (81.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Neutrophil count decreased									
Diarrhoea									
Nausea									
Hypokalaemia									
Hypoxia									
Aspartate aminotransferase increased									
Cough									
Alanine aminotransferase increased									
Hypophosphataemia									
Lymphocyte count decreased							-	-	-
Tachycardia									
Fatigue									
Hypocalcaemia				-	-	-			
Hypertension									
Pain in extremity									

Constipation									
Anxiety							-	-	-
Blood bilirubin increased									
Acute kidney injury									
Pulmonary oedema							-	-	-
Upper respiratory tract infection									
Abdominal pain									
Hypoalbuminaemia				-	-	-	-	-	-
Neutropenia							-	-	-
Back pain				-	-	-	-	-	-
Myalgia				-	-	-			
Hyperuricaemia				-	-	-			
International normalised ratio increased									
Nasal congestion				-	-	-			
Thrombocytopenia							-	-	-
Arthralgia				-	-	-			

Delirium				-	-	-	-	-	-
Disseminated intravascular coagulation				-	-	-	-	-	-
Encephalopathy				-	-	-			
Hyperglycaemia				-	-	-			
Pleural effusion									
Rhinovirus infection				-	-	-	-	-	-
Serum ferritin increased				-	-	-	-	-	-
Tachypnoea				-	-	-			
Blood creatinine increased	-	-	-						
Prothrombin time prolonged	-	-	-				-	-	-
Chills	-	-	-						
Epistaxis	-	-	-						
Hyperphosphataemia	-	-	-						
Rash	-	-	-						
Confusional state	-	-	-						

Sinus tachycardia	-	-	-						
Dizziness	-	-	-						
Haemoglobin decreased	-	-	-	-	-	-			
Lymphopenia	-	-	-	-	-	-			
Pain	-	-	-	-	-	-			
Activated partial thromboplastin time prolonged	-	-	-	-	-	-			
Rhinorrhoea	-	-	-	-	-	-			
Hyperbilirubinaemia	-	-	-	-	-	-			
Blood fibrinogen decreased	-	-	-	-	-	-			
Capillary leak syndrome	-	-	-	-	-	-			
Blood uric acid increased	-	-	-	-	-	-			
Procedural pain	-	-	-	-	-	-			
Metabolic acidosis	-	-	-	-	-	-			
Petechiae	-	-	-	-	-	-			
Sinusitis	-	-	-	-	-	-			

Insomnia	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Papular rash	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Contusion	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Dehydration	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Erythematous rash	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Generalised pruritus	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]

[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 (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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, [redacted], [redacted] and [redacted] patients experienced a tisagenlecleucel-related AE in the ELIANA, ENSIGN and B2101J trials, respectively.[47-49] 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 [redacted], 45 (77.6%) and [redacted] patients in the ELIANA, ENSIGN and B2101J trials, respectively.[47-49] In all three trials, the most common SAEs regardless of study drug relationship were CRS, febrile neutropenia and hypotension occurring in [redacted], [redacted] and [redacted] in ELIANA, [redacted], [redacted] and [redacted] in ENSIGN and [redacted], [redacted] and [redacted] in B2101J, respectively.[47-49] 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 23.

Table 23: 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=58)			B2101J (safety set) (N=56)[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	[redacted]	[redacted]	[redacted]	**45 (77.6)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Back pain	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Cardiac arrest	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Disseminated intravascular coagulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory distress syndrome	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Cardiac failure	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

Diarrhoea	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Encephalitis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Viral encephalitis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Gastroenteritis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Herpes zoster	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Mental status changes	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Multiple organ dysfunction syndrome	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pancreatitis	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Pneumonia	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Respiratory distress	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Respiratory syncytial virus infection	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Rhinovirus infection	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Septic shock	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Staphylococcal bacteraemia	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Tumour lysis syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Clostridium difficile infection	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Seizure	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Encephalopathy	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Clostridium difficile colitis	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Pulmonary oedema	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Capillary leak syndrome	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Dehydration	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Left ventricular dysfunction	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Coagulopathy	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Device related infection	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]
Headache	-	-	-	-	-	-	[redacted]	[redacted]	[redacted]

[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.
Abbreviations: CRS: cytokine release syndrome; NR: not reported; SAE: serious adverse event.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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, [redacted], [redacted] and [redacted] patients experienced a tisagenlecleucel-related SAE in the ELIANA, ENSIGN and B2101J trials, respectively.[47-49] 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, [redacted] patients had CRS.[47] The median time to onset of CRS was [redacted] days (range: [redacted] days). Of note, [redacted] cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[47]

Among the 61 patients with CRS, the median duration of CRS was [redacted] days (range: [redacted] days). [redacted] patients ([redacted]) were admitted to the intensive care unit (ICU) for a median duration of [redacted] days (range: [redacted] days) and a mean (SD) duration of [redacted] days. [redacted] patients ([redacted]) with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, siltuximab, corticosteroids or other therapies (e.g. infliximab, etanercept). One, two, and three doses of tocilizumab were required in [redacted], [redacted], and [redacted] patients, respectively, and [redacted] patients ([redacted]) received corticosteroids in addition to tocilizumab. [redacted] patients required high-dose vasopressors, [redacted] patients required invasive ventilation, and [redacted] patients required dialysis.[47]

ENSIGN

CRS in the ENSIGN trial was assessed via the Penn Grading Scale for CRS (PGS-CRS). Of the 58 patients infused with tisagenlecleucel, 47 (81.0%) had CRS. The median time to onset of CRS was 4.0 days (range: 1–20 days). Of note, [redacted] cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[48]

Among the 47 patients with CRS, the median duration of CRS was 8.0 days (range: 2–33 days). [redacted] patients ([redacted]) were admitted to the ICU for a median duration of 9.0 days (range: 1–27 days) and a mean (SD) duration of [redacted] days. Thirteen patients (27.7%) 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 [redacted], [redacted], and [redacted] patients, respectively, and [redacted] patients ([redacted]) received corticosteroids in addition to tocilizumab. Fourteen patients required high-dose vasopressors, six patients required invasive ventilation, and four patients required dialysis.[48]

B2101J

CRS in B2101J was assessed via the a modification of the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale. Of the [redacted] patients infused with tisagenlecleucel, [redacted] had CRS. The median time to onset of CRS was [redacted] days (range: [redacted] days). Of note, [redacted] cases of CRS were grade 3/4 CRS and none of the CRS events were fatal.[49]

Among the [redacted] patients with CRS, the median duration of CRS was [redacted] days (range: [redacted] days). Twenty patients ([redacted]) were admitted to the ICU for a median duration of [redacted] days (range: [redacted]) and a mean (SD) duration of [redacted] days. [redacted] patients ([redacted]) with CRS were treated with systemic anti-cytokine therapy such as tocilizumab, siltuximab, corticosteroids or other therapies. One or two, doses of tocilizumab were required in [redacted] and 5 [redacted] patients, respectively, and [redacted] patients ([redacted]) received corticosteroids in addition to tocilizumab. [redacted] patients required high-dose vasopressors, [redacted] patients required invasive ventilation, and none required dialysis.[49]

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) are ongoing. Additional data from ELIANA may become available in August 2018 (April 2018 data cut-off) hence these data are anticipated to become available during the appraisal process.

B.2.12 Innovation

As a CAR-T therapy, tisagenlecleucel represents a paradigm shift in the management of paediatric and young adult r/r B-cell ALL, providing a completely novel treatment approach in which the patient's own immune cells are genetically reprogrammed so that they can recognise and fight the cancer, potentially for a lifetime. It is provided as a one-time treatment; only a single infusion is required, in contrast to chemotherapy treatment options that require multiple recurrent treatment cycles, increase patient and healthcare system burden because of this, and are associated with high mortality. Furthermore, tisagenlecleucel is a treatment option that offers a durable response, clinically meaningful improvements in HRQoL, and the potential for a cure in patients who would otherwise have a very poor prognosis. Overall, these benefits have the potential to alleviate the impact of both patient and caregiver burden resulting from r/r B-cell ALL, and allow young patients the opportunity to go back to their daily lives and attend school, university and go into employment. For parents and caregivers specifically, both the physical and eocnomic burden of ALL can be a major source of anxiety and regular inpatient and outpatient visits often disrupt parent and caregivers' employment and diminish their productivity. The impact that the introduction of tisagenlecleucel could have on parents and caregivers is therefore substantial, and yet these benefits will not have been captured within the economic analysis.

Despite the high proportion of patients successfully treated for newly diagnosed paediatric and young adult ALL, there are no UK-specific guidelines for the treatment of patients who experience multiple relapsed disease. As described in Section B.1.3.2, for these patients, treatment options in UK clinical practice are limited to salvage chemotherapy (specifically FLA-IDA) and blinatumomab. Despite its use, no clinical evidence exists for the efficacy of FLA-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 FLA-IDA are poor, and can be considered comparable to those observed with clofarabine monotherapy. This has been shown to be less than 3 months in this patient population and the rate of CR was 30%,[2, 34] whilst blinatumomab is associated with median OS of only 7.5 months and a CR rate of only 39%.[34, 35] Patients up to 25 years of age with ALL that is refractory, in relapse post-transplant, or in second or later relapse therefore have extremely limited

treatment options, with a lack of licensed therapies and a paucity of published data informing their efficacy. Many of these patients are instead often enrolled into experimental clinical trials when all other treatment possibilities have been exhausted. The prognosis of these patients also worsens with each subsequent relapse, highlighting a considerable unmet need for new treatments offering both durable responses and the hope for a cure.[30]

In the ELIANA, ENSIGN and B2101J trials, tisagenlecleucel demonstrated high tumour remission rates and sustained DoR.[47-49] In the ELIANA trial specifically, [redacted] of the patients who achieved a BOR of CR/CRi had MRD-negative disease, a strong prognostic factor and robust indicator of relapse, indicating a reduced risk of further relapses following infusion with tisagenlecleucel.[47, 66] Moreover, median OS in the pooled analysis was [redacted] months, a truly compelling result considering median OS with currently used regimens in the r/r setting ranges from less than 3 months to 7.5 months.[34, 35, 47] Longevity of remission was also demonstrated, with median DoR not reached in ELIANA at the current data cut-off (31st Dec 2017), [redacted] of patients still in remission at Month 6 and [redacted] at Month 12.[47] These data are also still relatively immature, and these results could further improve once more data becomes available.

The potential benefits of tisagenlecleucel as an innovative therapy for a condition with considerable unmet need have been recognised by the US Food and Drugs Administration (FDA) and the EMA. The FDA awarded tisagenlecleucel "Breakthrough Therapy" designation and Priority Review for this indication,[76] and the EMA also granted tisagenlecleucel a PRIME designation and Accelerated Assessment in this indication.[77] Additionally, following FDA approval in August 2017, this was the first instance of FDA approval of a CAR-T therapy worldwide, demonstrating the revolutionary nature of tisagenlecleucel in this indication and the introduction of a pioneering treatment approach in oncology.[9]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 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 ongoing, single-arm and open-label studies.[57-59] At the time of the latest data cut-off dates presented within this submission, [redacted] paediatric and young adult patients with r/r B-cell ALL had received an infusion with tisagenlecleucel.[47-49] 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. The principal findings from the ELIANA, ENSIGN and B2101J trials are discussed below.

The ELIANA trial met its primary endpoint at the first interim analysis (data cut-off 17th August 2016), and at the current data cut-off (31st Dec 2017), the ORR within 3 months post-tisagenlecleucel infusion in [redacted] patients was [redacted] (95% CI: [redacted]). In addition, [redacted] patients with a BOR achieved MRD-negative disease, a reliable indicator of reduced risk of further relapses. Responses were also highly durable, with median DoR, EFS and OS not yet reached.[47] Consistent with this, in the ENSIGN trial (data cut-off 6th Oct 2017), the primary objective was also met with an ORR during the 6 months post-tisagenlecleucel infusion of 69.0% (95% CI: 52.9, 82.4), as well as demonstrating robustness in sensitivity analyses. MRD-negative disease was also achieved in 93.1% of patients achieving CR or CRi, consistent with a deep and meaningful response. Durable responses are evident, with median DoR not yet reached and median EFS of

[redacted] months (95% CI: [redacted]). Median OS was 23.8 months (95% CI: 8.8, NE).[48] Lastly, results from B2101J (data cut-off 30th Jan 2017) demonstrate that after long-term follow-up of up to [redacted] months, tisagenlecleucel is consistently efficacious in the treatment of paediatric and young adult patients with r/r B-cell ALL. ORR at Day 28 post-tisagenlecleucel infusion was very high at [redacted] (95% CI: [redacted]), with [redacted] patients achieving a CR/CRi with MRD negative disease. Median DoR was [redacted] months, median EFS [redacted] months and median OS [redacted] months.[49] Although pharmacokinetic data is not presented within this submission, the persistence of tisagenlecleucel supports the longevity of response.

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 [redacted], [redacted] and [redacted] patients in ELIANA, ENSIGN and B2101J, respectively. In almost all cases, development of CRS occured 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.[47-49] 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. This again 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 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 FLA-IDA, and therefore no MAIC was conducted specifically for tisagenlecleucel versus FLA-IDA. Instead, the efficacy of clofarabine monotherapy from the study by Jeha *et al.* (2006) were used as a proxy for the efficacy of FLA-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.

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.[49, 76, 77]

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.[78, 79] Furthermore, the patient population treated with tisagenlecleucel is large, at [redacted] patients, particularly considering the rare nature of paediatric and young adult r/r B-cell ALL. Together with the long-term follow-up available from the B101J trial (almost 5 years), the pooled data for all three trials provides evidence which can be considered to reliably demonstrate the quality and longevity of responses following tisagenlecleucel, in a relatively large and representative patient population. In addition, the robustness of the data presented here is compelling, especially given the size of our target population, and the rare nature of 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. ELIANA, ENSIGN and B2101J are single-arm studies and tisagenlecleucel has not been included as part of an RCT. In order to provide estimates of the relative effectiveness of tisagenlecleucel versus salvage chemotherapy regimens, MAICs were conducted based on the individual patient-level data (IPD) from the pooled tisagenlecleucel studies and summary data from von Stackelberg *et al.* (2016) for blinatumomab and Jeha *et al.* (2006) for salvage chemotherapy (FLA-IDA), based on the guidance provided in the NICE Decision Support Unit (DSU): Technical Support Document (TSD) 18.[80]

The eligibility criteria of all three tisagenlecleucel clinical trials are well-matched to the decision problem outlined in the final scope for this appraisal. The majority of patients in ELIANA, ENSIGN and B2101J were treated with tisagenlecleucel in the US, with no UK centres in clinical trials thus far. However, all three trials 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.[2] There is consistency in the safety and efficacy outcomes between ELIANA, a trial based in several different countries including the EU and Australia, compared to ENSIGN and B2101J (US-only trials). This suggests that the outcomes associated with tisagenlecleucel are reproducible between countries and can be generalisable to the eligible patient population of tisagenlecleucel in UK clinical practice.

B.2.14 End-of-life criteria

It is evident that tisagenlecleucel meets NICE's end-of-life criteria in this indication and a summary of the available supporting evidence is presented in Table 24.

Table 24: End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Median OS with blinatumomab is 7.5 months (95% CI: 4.0 to 11.8 months).[35] This was observed in the study by von Stackelberg *et al.* (2016), of 70 paediatric patients <18 years with ALL that was primary refractory, in first relapse, after full salvage induction regimen, in second or later relapse, or in any relapse after allo-SCT • Feedback from UK clinical experts was that: o 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 o In the second relapse setting, survival with blinatumomab is undoubtedly <2 years; very few	Section B.2.9

	patients would survive for more than two years; a 2nd allo-SCT could provide hope for patients in this situation but this is not actually available for all patients • A further expanded access study of blinatumomab has been identified, the RIALTO study, in which median overall survival was 9.8 months (95% CI: 7.1-NE).[75] • Median OS with clofarabine chemotherapy, the efficacy of which can be considered as a proxy for salvage chemotherapy (specifically FLA-IDA), was 13 weeks in the Jeha *et al.* (2006) study.[34] • Given that the prognosis of patients with ALL is deemed to differ only between those patients <30 and those >30 years old, it is expected that patients within the full licensed indication of tisagenlecleucel (aged up to 25) would be associated with the same prognosis as patients <18 years old. This is supported by evidence in the adult population with blinatumomab, where median OS was 7.7 months (95% CI: 5.6 to 9.6 months)[46] • Furthermore, median OS with various salvage chemotherapies in the adult population was 3.9 months (95% CI: 2.8-4.9) in the study by Kantarjian *et al.* (2017)[46] • Based on previous technology appraisals in the adult ALL population, the Committee accepted that both blinatumomab and inotuzumab met NICE's end-of-life criterion for short life expectancy based on median OS[44, 81] • As such, it is evident that tisagenlecleucel is indicated for patients with a life expectancy of normally less than 24 months	
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Median OS from the latest data cuts of the three tisagenlecleucel clinical trials is as follows: o ELIANA: [redacted] with a maximum OS follow-up of [redacted] months[47] o ENSIGN: 23.8 months (95% CI: 8.8 to NE) with a maximum OS follow-up of [redacted] months[48] o B2101J: [redacted] with a maximum OS follow-up of [redacted] months[49] • In the absence of head-to-head data, a direct comparison cannot be made to assess whether tisagenlecleucel extends life compared to current treatment by 3 months. However, as can be seen from a naïve comparison with the median OS results of all three trials, the length of survival with tisagenlecleucel is well beyond the 7.5 months observed with blinatumomab, and the ~3 months observed with salvage chemotherapy regimens.[34, 35]	Section B.2.8

Abbreviations: CI: confidence interval; NE: not estimable; NHS: National Health Service; OS: overall survival.
Source: ELIANA CSR (31st Dec 2017); ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan);[49] Jeha *et al.* (2006);[34] Kantarjian *et al.* (2017);[46] Locatelli *et al.* (2017);[75] von Stackelberg *et al.* (2016).[35]

B.3 Cost-effectiveness

Summary of cost-effectiveness

- A de novo cost-utility model was developed to evaluate the cost-effectiveness of tisagenlecleucel as a treatment 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. The model adopted a partitioned survival approach with three health states: *event free, relapsed/progressed disease*, and *death*. A decision tree was also included to account for patients who may not ultimately receive tisagenlecleucel due to manufacturing failure, AEs or death post leukapheresis but prior to infusion.
- Tisagenlecleucel was compared to blinatumomab using clinical efficacy data from the study by von Stackelberg *et al.* (2016) and salvage chemotherapy (FLA-IDA) using clinical efficacy data from a clofarabine monotherapy study (Jeha *et al.* [2006]) as a proxy.
- Given the potential for tisagenlecleucel to offer a potential 'cure', OS and EFS estimates were extrapolated using a mixture cure model approach. This approach was also used for blinatumomab; for salvage chemotherapy, a standard parametric survival approach was used.
- Utility values for the *event-free* and *relapsed/progressed disease* states were derived from the study by Kelly *et al.* (2006); disutilities for treatment, AEs and ICU were also included.
- Resource use and costs included in the model were based on information from the ELIANA trial, previous technology appraisals and appropriate published sources including the BNF, the eMIT and NHS reference costs 2016–2017.
- Extensive feedback from several UK clinical experts 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 salvage chemotherapy (FLA-IDA) and blinatumomab.
- Under the base case assumptions, tisagenlecleucel (at list price) was associated with ICERs of [redacted] and [redacted] versus salvage chemotherapy (FLA-IDA) and blinatumomab, respectively. When provided with the confidential PAS discount ([redacted]), the ICERs were £25,404 and £18,392, respectively; these ICERs are below the cost-effectiveness threshold of £30,000 per QALY and well below the cost-effectiveness threshold of £50,000 per QALY considered appropriate for therapies meeting end-of-life criteria.

Sensitivity analyses

- ICER estimates obtained from 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 deterministic sensitivity analysis (DSA), the EFS utility value and the rate of subsequent allo-SCT were found to be the most influential parameters on the ICERs.
- Scenario analyses were conducted to explore the impact of alternative parametric distributions for OS and EFS, alternative efficacy inputs, alternative decision tree inputs amongst. In all of the scenario analyses conducted, the ICERs for tisagenlecleucel (with PAS) were found to be well below a cost-effectiveness threshold of £50,000 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 in December 2017 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 three potentially relevant cost-effectiveness studies and a further three economic evaluations were identified via supplementary manual searches.[82-87] A summary of the six records included in the SLR for cost-effectiveness studies is presented in Table 25, with further details presented in Appendix G.

Table 25: Summary list of published cost-effectiveness studies

Study	Country (Year)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Lis 2012[87]	Poland (2012)	A simulation method using a decision- tree with lifetime time horizon determined at the level of life expectancy	Children and adolescents with r/r B-cell ALL who have received at least two prior standard lines and in case there are no other options enabling to predict a long- term response (as a third- line therapy, used among patients qualified for hematopoietic stem cell transplantation)	Clofarabine combination therapy versus nelarabine: 2.66 Versus FLAG-IDA: 2.55	Clofarabine combination therapy versus nelarabine: 86,715 PLN Versus FLAG-IDA: 77,356 PLN	Clofarabine combination therapy versus nelarabine: 27,529 PLN Versus FLAG-IDA: 26,046 PLN
Snider 2017[85]	UK (2016)	Expanded upon the NICE model[a]	Paediatric patients with r/r B-cell ALL	Tisagenlecleucel versus clofarabine: 10.1	NR	NR
Hao 2017[86]	US (2016)	A partitioned survival model with monthly cycle. The model included three health states: EFS, progressive disease, and death	Paediatric and young adult patients with r/r B-cell ALL	Tisagenlecleucel versus clofarabine monotherapy: 4.29 Versus clofarabine combination therapy: 3.64 Versus blinatumomab: 3.64 Versus salvage chemotherapy: 2.32 Versus allo-SCT: 2.31	NR	NR
ICER CAR-T Draft Evidence Report[83]	US (2017)	A two-part model with life time horizon, consisting of a short-term decision tree and long-term semi-Markov partitioned survival model	Patients aged 0–25 years with relapsed/refractory B-cell ALL	Versus clofarabine: 7.18	Versus clofarabine: $329,498	Versus clofarabine: $45,871
NICE CAR-T Mock Appraisal[84]	UK (2015)	• Bridge to allo-SCT: a decision tree model (day 0 to 56) and a series	Children and young adults with two or more relapses or refractory ALL	-	-	Versus standard of care (clofarabine): £55,090

		of partitioned survival models (day 56 to lifetime) with a life time horizon • Curative intent: Partitioned survival model with a life time horizon				
pCODR Report[82]	Canada (2017)	Partitioned-survival model with a life time horizon (95 years)	Paediatric patients with relapsed/refractory Ph-ve ALL	Blinatumomab versus salvage chemotherapy: • Manufacturer's submission – 4.26 • EGP reanalysis[b] lower bound – 7.38 • EGP reanalysis upper bound – 1.11	Blinatumomab versus salvage chemotherapy: • Manufacturer's submission – $67,913 • EGP reanalysis lower bound – $48,572 • EGP reanalysis upper bound – $112,363	Blinatumomab versus salvage chemotherapy: • Manufacturer's submission – $15,940 • EGP reanalysis lower bound – $6,557 • EGP reanalysis upper bound – $100,948

[a]NICE (2017).[88] [b]The EGP reanalysed the estimates to highlight the uncertainty around lack of comparative effectiveness data, small sample size for efficacy data for blinatumomab, historical comparator and duration of treatment with blinatumomab.
Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: allogeneic haematopoietic stem cell transplantation; CAR-T: chimeric antigen receptor T-cell; EFS: event-free survival; EGP: Economic Guidance Panel; FLAG-IDA: fludarabine, cytarabine, G-CSF and idarubicin; ICER: incremental cost-effectiveness ratio/institute for clinical and economic review; NICE: National Institute for Health and Care Excellence; pCODR: pan-Canadian Oncology Drug Review; Ph-ve: Philadelphia chromosome negative; PLN: Polish zloty; QALY: quality-adjusted life year; r/r: relapsed/refractory.
Source: Lis *et al.* (2012);[87] Snider *et al.* (2017);[85] Hao *et al.* (2017);[86] ICER (2017);[83] Hettle *et al.* (2015);[84] pCODR (2017).[82]

B.3.2 Economic analysis

A *de novo* cost-effectiveness model was constructed for the economic analysis, as described in the following sections.

B.3.2.1 Patient population

The patient population for the economic analysis comprised patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. This patient population is in line with the expected 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 1). The patient population is also consistent with the patient population evaluated across all three tisagenlecleucel clinical trials in r/r B-cell ALL: ELIANA, ENSIGN and B2101J.[57-59]

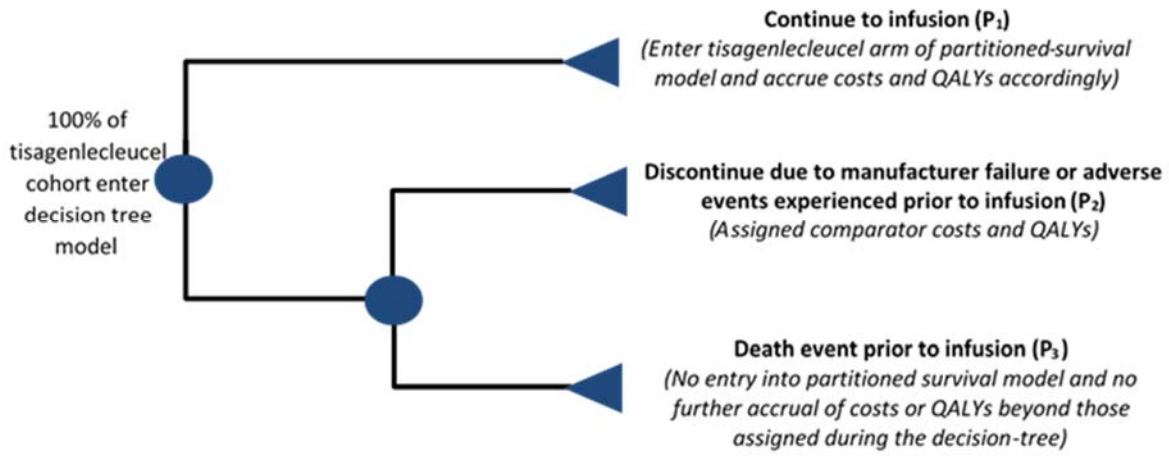
B.3.2.2 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of tisagenlecleucel versus relevant comparators in 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 developed model was a cohort-based partitioned survival model 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 clinical pathway of care for 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 (TA405 and ID893).[44, 81] In addition to the partitioned survival model, the model structure included a decision tree prior to entry into the partitioned survival model 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 clinical trials of tisagenlecleucel and the potential for this is a feature of the unique manufacturing and administration process for tisagenlecleucel. However, it should be noted that as the manufacturing process is refined, and the manufacturing capacity increases, the proportion of patients in clinical practice who, after being assigned for treatment with tisagenlecleucel may not ultimately receive infusion is anticipated to reduce in the future.

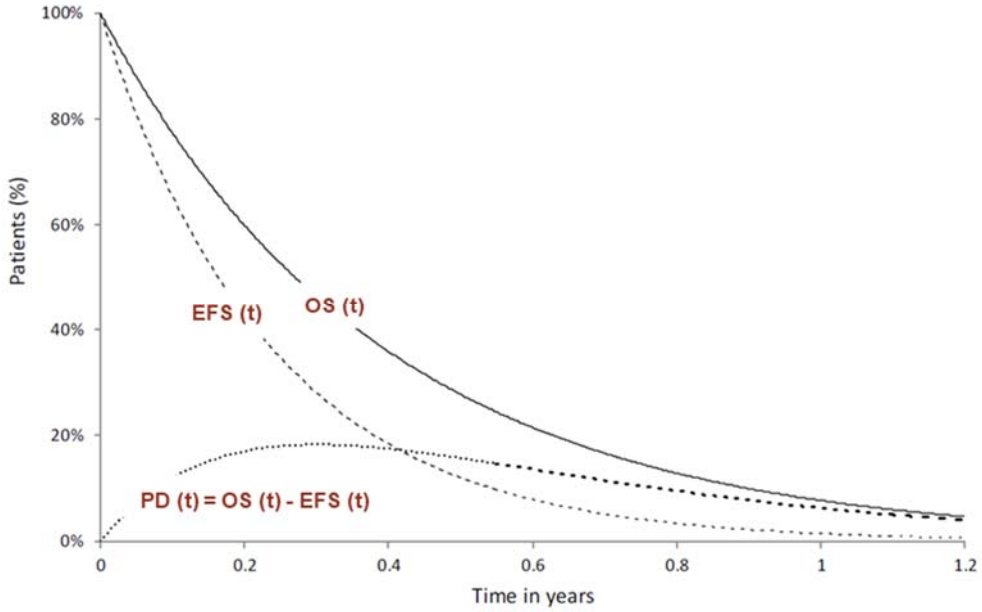
The decision tree element of the model, applied to the tisagenlecleucel arm only, is presented in Figure 25. A graphical depiction of the partitioned survival model approach is presented in Figure 26.

Figure 25: Decision tree structure for tisagenlecleucel cohort



Abbreviations: QALYs: quality-adjusted life years.

Figure 26: Partitioned survival modelling approach



Abbreviations: EFS: event-free survival; OS: overall survival; PD: progressed disease.

Decision tree prior to partitioned survival model entry

The process of treatment with tisagenlecleucel is described in Table 2 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 may be administered bridging chemotherapy in order to stabilise their disease whilst waiting for tisagenlecleucel manufacturing, as was done in the ELIANA, ENSIGN and B2101J trials.[57-59] 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 draft Summary of Product Characteristics in the reference pack).[1]

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, therefore 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 and would be associated with different outcomes and costs 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 25:

- A proportion of patients (P_1) will successfully proceed to infusion with tisagenlecleucel. These patients therefore enter the partitioned survival model 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 salvage chemotherapy (FLA-IDA) and blinatumomab for this proportion of tisagenlecleucel patients. In line with the market share estimates for salvage chemotherapy (FLA-IDA) and blinatumomab in current clinical practice, it was assumed that 50% of this proportion of patients would revert to receive salvage chemotherapy (FLA-IDA) and 50% would revert to receive blinatumomab. 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.3.2.3.

As the comparator therapies (salvage chemotherapy [FLA-IDA] and blinatumomab) included within the economic analysis are not associated with the same process as described above for tisagenlecleucel, they are therefore not associated with the potential feature 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 partitioned survival model 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 acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse was modelled to enter the partitioned survival model in the EFS health state and to receive either tisagenlecleucel or a comparator therapy (salvage chemotherapy [FLA-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 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.[89] The death health state is an absorbing health state. 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. Importantly, the EFS and OS curves can be constructed from summary Kaplan-Meier data in the absence of individual patient-level data (IPD). IPD data 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. Finally, as noted above, the partitioned survival model structure has previously been used in previous economic models submitted to NICE in r/r B-cell ALL (TA450 and ID893).[44, 81]

Features of the *de novo* analysis

OS and EFS data for tisagenlecleucel were derived from a pooled analysis of all three tisagenlecleucel clinical trials: ELIANA, ENSIGN and B2101J.[47-49] Full details of the clinical efficacy sources for tisagenlecleucel and the relevant comparators are provided in 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 effectiveness estimates were discounted at 3.5% annually. A summary of the key features of the *de novo* economic analysis and their justification is provided in Table 26. 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 blinatumomab and inotuzumab adult appraisals was made.

Table 26: Features of the economic analysis

	Blinatumomab	Inotuzumab	Current appraisal	
Factor			**Chosen values**	**Justification**
Time horizon	Lifetime horizon (50 years)	Lifetime horizon (60 years)	Lifetime horizon (88 years)	The reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Clinical parameters	• Clinical parameters (response, EFS and OS) used in the economic model base case were derived from the TOWER RCT[46] • 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[90] • It was assumed that people who survived more than 60 months (five years) were cured	• Clinical parameters (EFS and OS) for tisagenlecleucel used in the economic model were derived from the ELIANA, ENSIGN and B2101J clinical trials[57-59] • 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 and blinatumomab. Mixture cure models for salvage chemotherapy were implausible; therefore a standard parametric model was used with an assumption that people survived more than 60 months (five years) were cured	Clinical trial data is the most appropriate source to estimate the effectiveness of the interventions in question
Source of utilities	NR	NR	• EFS: 0.91 • PD: 0.75 Kelly *et al.* (2015)	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). This study was used as the source of utility values in the NICE mock appraisal of regenerative therapies.

Source of costs	• NHS Reference Costs • PSSRU • BNF/eMIT	• NHS Reference Costs • PSSRU • BNF/eMIT	• NHS Reference Costs • PSSRU • BNF/eMIT	NHS Reference Costs, PSSRU, BNF and eMIT are standard sources of UK-relevant costs and were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature.

Abbreviations: BNF: British National Formulary; DLBCL: diffuse large B-cell lymphoma; DSU: Decision Support Unit; 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; SF-36: Short Form Health Survey; TSD: Technical Support Document.

B.3.2.3 Intervention technology and comparators

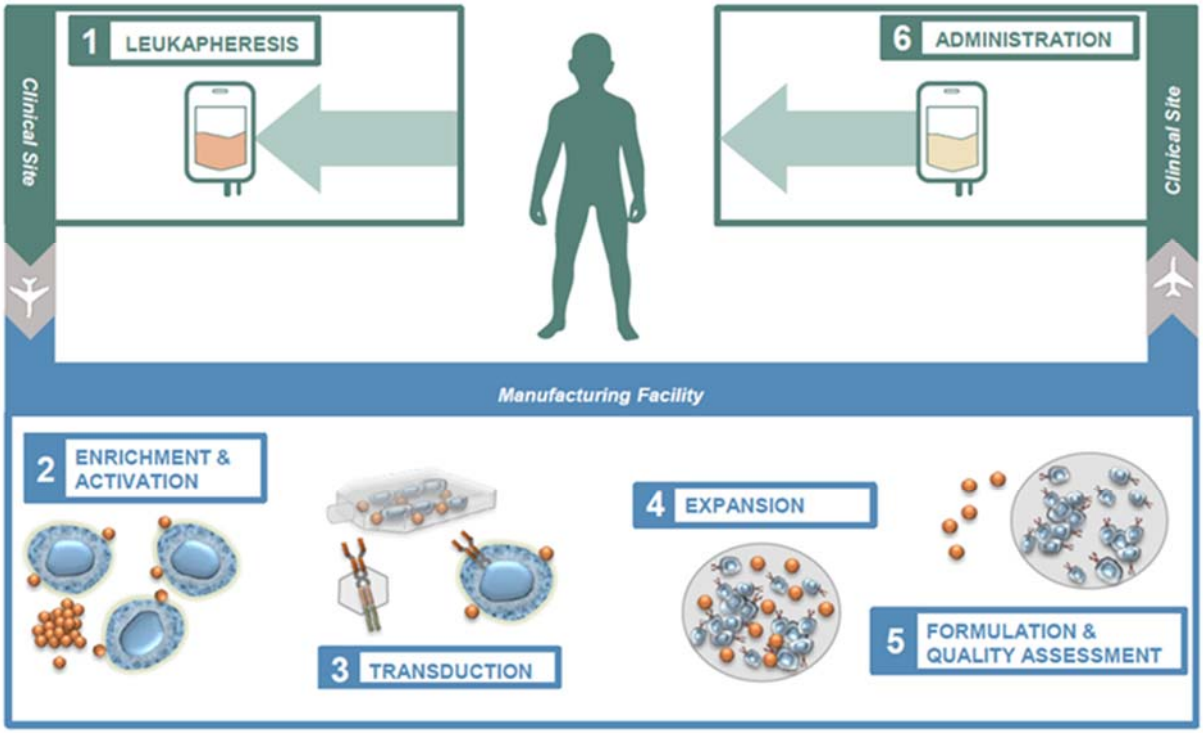
Intervention: tisagenlecleucel

Tisagenlecleucel is provided as a single, one-time treatment for iv use only. For paediatric and young adult patients with r/r B-cell ALL, tisagenlecleucel is recommended at the following doses (see the draft Summary of Product Characteristics provided in the reference pack of this submission):[1]

- 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)

Manufacturing of the CAR-positive viable T-cells requires a step-by-step process as outlined in Figure 27 and there are three pre-treatment phases that patients undergo prior to receiving infusion with tisagenlecleucel: leukapheresis, bridging chemotherapy (where appropriate) and lymphodepleting chemotherapy.

Figure 27: Summary of the manufacturing and administration process for tisagenlecleucel



Source: Novartis Pharmaceuticals UK Ltd.

Bridging chemotherapy

As described in Section B.3.2.2, whilst the manufacturing process of tisagenlecleucel is taking place following leukapheresis, patients may be administered bridging chemotherapy in order to stabilise their disease, followed by a course of lymphodepleting chemotherapy prior to tisagenlecleucel infusion.

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 in all three trials. As such, the bridging chemotherapy regimen incorporated within the economic model was based on feedback from UK clinical experts, who stated that

patients would typically receive the following bridging chemotherapy regimen in the outpatient setting.[2] Given the current manufacturing time of tisagenlecleucel is [redacted], it was assumed that patients received bridging chemotherapy for a total of 3 weeks as follows:

- Allopurinol 100 mg/m^2 orally three times daily for 5 days
- Dexamethasone 6 mg/m^2/day for 14 days then dexamethasone 3 mg/m^2/day for 7 days
- Vincristine 1.5 mg/m^2 iv weekly for 3 weeks
- Intrathecal methotrexate 12 mg on days 1 and 8
- Co-trimoxazole 480 mg orally twice daily for two consecutive days each week for 3 weeks

The proportion of patients who received infusion with tisagenlecleucel that were assumed to receive bridging chemotherapy was [redacted] based on pooled data from ELIANA (25th Apr 2017) and ENSIGN (6th Oct 2017) (data from the latest ELIANA cut-off or B2101J were not available). 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. Furthermore, the manufacturing time for tisagenlecleucel may reduce even further as the manufacturing process is refined; as such, in clinical practice, patients may receive bridging chemotherapy for a shorter duration of time than is estimated in the base case economic analysis.

Lymphodepleting chemotherapy

As stated in the draft 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.[1] 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 draft SmPC and therefore both regimens were included within the economic model:[1]

- Regimen 1: 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); or
- Regimen 2: 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.*

It was assumed that [redacted] of patients who received infusion with tisagenlecleucel received lymphodepleting chemotherapy based on pooled data from all three tisagenlecleucel clinical trials: ELIANA (25th Apr 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017).[50] 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 proportions of patients who were modelled to actually receive infusion with tisagenlecleucel and the associated pre-treatment therapies within the decision tree part of the model are as follows, and can all be user-modified within the economic model on the "Specification" tab:

- P_1 successfully proceed to infusion with tisagenlecleucel = [redacted] based on the proportion of enrolled patients from all three tisagenlecleucel clinical trials: ELIANA (31st

Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017) who underwent tisagenlecleucel infusion (excluding 4 patients pending infusion in ENSIGN)[47-49]

- Proportion of these patients assumed to receive bridging chemotherapy: [redacted] based on pooled data from ELIANA (25th Apr 2017) and ENSIGN (6th Oct 2017) (data from the latest ELIANA cut-off or B2101J were not available)
- Proportion of these patients assumed to receive lymphodepleting chemotherapy: [redacted] based on pooled data from all three tisagenlecleucel clinical trials: ELIANA (25th Apr 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017) (data from the latest ELIANA cut-off were not available)

- P_2 do not receive 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 = [redacted] ([redacted]) based on the proportion of enrolled patients from from all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017) who had not received tisagenlecleucel infusion due to manufacturing failure or AEs (or other, e.g. administration failure)[47-49]
  - Proportion of these patients assumed to receive bridging chemotherapy: 50%
  - Proportion of these patients assumed to receive lymphodepleting chemotherapy: 50%

- P_3 death prior to tisagenlecleucel infusion = [redacted] ([redacted]) based on the proportion of enrolled patients from the ELIANA, ENSIGN and B2101J trials (31st Dec 2017, 6th Oct 2017, 30th Jan 2017 data cut-offs, respectively) who had not received tisagenlecleucel infusion due to death[47-49]
  - Proportion of these patients assumed to receive bridging chemotherapy: 50%
  - Proportion of these patients assumed to receive lymphodepleting chemotherapy: 50%

Patients who did not receive tisagenlecleucel either due to failure in manufacture of the tisagenlecleucel product or due to experiencing an AE that rendered them unsuitable to continue to tisagenlecleucel infusion were instead assumed to receive one of the comparator therapies i.e. either salvage chemotherapy (FLA-IDA) or blinatumomab (in a 1:1 ratio as described in Section B.3.2.2). Details of the comparator therapies included within the economic model are described below.

It should be noted that P_1 – the proportion successfully proceeding to infusion with tisagenlecleucel – is anticipated to be higher in the commercial setting. The probabilities P_1, P_2 and P_3 were based on the proportions of patients experiencing manufacturer failure and other events preventing them proceeding to infusion in the clinical study setting. It is anticipated that with ongoing commercial usage of tisagenlecleucel and increased manufacturing experience, the rate of manufacturer failure would decrease over time. The base case analysis therefore likely underestimates the proportion of patients successfully proceeding to tisagenlecleucel infusion versus that which is expected to be realised in clinical practice. A scenario analysis explored an assumption that 100% of patients proceed to infusion with tisagenlecleucel.

Comparators: salvage chemotherapy (FLA-IDA) and blinatumomab

Salvage chemotherapy (FLA-IDA)

Feedback from several 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 FLA-IDA (fludarabine, cytarabine and idarubicin).[2] As such, the costs of salvage chemotherapy within the model were based on the drug acquisition and administration costs associated with treatment with the FLA-IDA regimen.

The dosing regimen of FLA-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:[2, 91]

- Fludarabine 30 mg/m^2 daily for 5 doses
- Cytarabine 2 mg/m^2 daily for 5 doses
- Idarubicin 8 mg/m^2 daily for 3 doses.

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):[35]

- Cycle 1 (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–7: 5 mcg/m^2/day
    - Days 8–28: 15 mcg/m^2/day
- Cycle 2 and subsequent cycles (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–28: 15 mcg/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 budget impact analysis template).

The dose of blinatumomab for patients over the age of 18 was based on the blinatumomab SmPC.[92]

- Cycle 1 (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–7: 9 mcg/m^2/day
    - Days 8–28: 28 mcg/m^2/day
- Cycle 2 and subsequent cycles (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–28: 28 mcg/m^2/day

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 27. These were presented to UK clinical experts who agreed with

consensus that the rates of subsequent allo-SCT for each treatment were considered in line with what would see in clinical practice. The costs associated with patients receiving a subsequent allo-SCT included in the model are described in Section B.3.2.3.

Table 27: Proportion of patients receiving subsequent allo-SCT in the model

Intervention	Rate of subsequent allo-SCT	Source
Tisagenlecleucel	[redacted]	Pooled tisagenlecleucel clinical trials (ELIANA [31st Dec 2017]; ENSIGN [6th Oct 2017]; B2101J [30th Jan 2017])[47-49]
Salvage chemotherapy (FLA-IDA)	16.39%	Jeha *et al.* (2006)[34]
Blinatumomab	34.29%	Von Stackelberg *et al.* (2016)[35]

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

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The patients baseline characteristics for the modelled cohort are provided in Table 28 and were based on the pooled baseline characteristics of patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=[redacted]) in all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017).[47-49]

As discussed in Section B.2.3.3 and Section B.2.8, the patient baseline characteristics of all three tisagenlecleucel clinical trials were considered comparable thus supporting a pooled analysis. This approach was validated by four UK clinical experts who reviewed the pooled patient baseline characteristics from all three trials and considered them to be representative of the tisagenlecleucel-eligible patient cohort in UK clinical practice.[2] Furthermore, in order to increase the available sample size and enable the inclusion of the longest-term follow-up data from the B2101J trial, the clinical efficacy inputs used to inform the base case analysis were also based on the pooled analysis of all three tisagenlecleucel clinical trials (see Section B.3.3.2). It was therefore considered most appropriate to also use the pooled patient baseline characteristics from all three tisagenlecleucel clinical trials in the base case analysis.

The mean age and the percentage female were used alongside England and Wales life tables (2014–2016) 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 28: Patient baseline characteristics of the base case economic analysis

Model parameter	Value	Source
Mean age	[redacted]	ELIANA, ENSIGN and B2101J
Percentage female	[redacted]	ELIANA, ENSIGN and B2101J
Average BSA	[redacted]	ELIANA and ENSIGN (height IPD were not available from the B2101J trial and therefore average BSA could not be calculated for this trial)

Average body weight	[redacted]	ELIANA, ENSIGN and B2101J

Abbreviations: BSA: body surface area; IPD: individual patient-level data.
Source: ELIANA CSR (31st Dec 2017);[47] ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017).[49]

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 a pooled analysis of patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=[redacted]) in all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017).[47-49] The IPD from each trial were combined directly without adjustment to derive the pooled OS and EFS estimates of tisagenlecleucel.

A summary of the pooled analysis of all three tisagenlecleucel clinical trials is presented in Section B.2.8. Overall, it was considered that the baseline characteristics of the patients across all three trials were sufficiently similar and that any differences in trial design would not be expected to impact the outcomes of each trial; therefore, it was considered appropriate to pool the data available from all three clinical trials. Furthermore, the eligibility criteria of all three clinical trials match the intended patient population for tisagenlecleucel in UK clinical practice.[2] As such, the pooling of data from all three clinical 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 receive tisagenlecleucel in UK clinical practice. Finally, the pooled analysis enables the inclusion of the longest-term follow-up data from the B2101J trial which is almost 5 years (maximum follow-up [redacted] months) to help reduce any uncertainties in the long-term extrapolation of the trial data.[49]

Salvage chemotherapy (FLA-IDA) and blinatumomab

As all three clinical trials of tisagenlecleucel were designed as single-arm trials 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 (FLA-IDA) and 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 B.2.9, the SLR identified two published studies of blinatumomab in paediatric patients aged up to 18 years with r/r B-cell ALL: a phase II clinical trial (n=70) published by von Stackelberg *et al.* (2016) and an expanded open-access study (n=40) published as a poster at the American Society of Clinical Oncology conference 2017 (the RIALTO study).[35, 75] 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 and the larger of the two identified clinical trials for blinatumomab.[35] 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. The OS data from von Stackelberg *et al.* (2016) alone were therefore used in the base case analysis. However, in recognition of the availability of the data from the RIALTO study, the use of the RIALTO study to inform the clinical efficacy for blinatumomab was explored as part of a scenario analysis (see Section B.3.8.3).[75]

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 FLA-IDA). As such, in order to model the efficacy of salvage chemotherapy (FLA-IDA), OS data from a study of clofarabine monotherapy published by Jeha *et al.* (2006) were used as a proxy.[34] This assumption was validated by four UK clinical experts, 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 (FLA-IDA) in UK clinical practice.[2]

The use of three further possible sources of clinical evidence to inform the efficacy of salvage chemotherapy (FLA-IDA) within the economic model were explored in scenario analyses.[46, 93]

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, though clinical experts indicated that it would be difficult to draw any conclusions as to the likely direction of any bias introduced by any differences in the patient populations. As noted in Section B.2.9, a MAIC was conducted in order to explore adjustments of the pooled 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 estimates.[34, 35] Ultimately, the MAICs found that the resulting adjustments to the tisagenlecleucel OS profile were modest in nature. The 95% confidence intervals of the adjusted ('matched') tisagenlecleucel curves were found to overlap 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 23 and Figure 24 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. A scenario analysis explored the use of the matched OS data (see Section B.3.8.3) and found it to have a very minimal impact on the ICERs.

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 (pooled ELIANA, ENSIGN and B2101J for tisagenlecleucel; Jeha *et al.* (2006) for salvage chemotherapy (FLA-IDA); and von Stackelberg *et al.* (2016) for blinatumomab – see Sections B.2.8 and B.2.9) were shorter than the model time horizon, extrapolation from the observed OS and EFS data was required.[34, 35, 47-49]

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) and flexible models (i.e. spline models) were explored for extrapolation.[94] For the spline models, these were developed based on the algorithm by Royston and Parmar *et al.* (2002).[95] A series of one-, two-, three-, and four-knot cubic spline models expressed on the proportional hazard scale were considered, with the knot locations chosen at quantiles of the log uncensored death times in the study, as per the default settings for the FlexSurv package in R. 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. It is well-established that standard parametric survival models are limited in their use for modelling hazard functions that follow more complex patterns.[96] 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.[96, 97]

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 the same risk of death as the general population, and one representing non-cured patients, who have a risk of death as defined by a parametric survival model.

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 supported by a number of observations.

- Firstly, the OS data from the clinical studies of tisagenlecleucel presented in Section B.2 is associated with a plateau that represents a clear feature of the hazard function over time, and is indicative of the existence of a proportion of patients being associated with long-term survival. For study B2101J, which represents the study with the longest follow-up, a plateau is evident from approximately 32 months with no further deaths observed beyond this point amongst patients remaining in study follow-up. In both the ELIANA and ENSIGN studies, similar plateaus have been observed: in ELIANA, no deaths have been observed beyond 19 months amongst those patients remaining in trial follow-up; in ENSIGN, a plateau is seen from approximately 24 months, with no patients who remained in follow-up beyond this point reported to have died. Although longer trial follow-up is required to provide support for the continuation of this plateau in the longer-term, the pooled trial data together provides data up to almost 5 years of follow-up (it should be noted that this represents substantially longer follow-up than for either of the comparator therapies). Furthermore, 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 potentially offering a cure. It is also supported on a mechanistic level by the observation of a similar plateau in the EFS data for tisagenlecleucel, 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.
- Outside of the considerations of the potentially 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.[44] 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.[88] Feedback from UK clinical experts experienced in the treatment of r/r B-cell ALL in the paediatric and young adult setting was sought in the context of this submission, and this 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.[2]

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 general population mortality as per the England and Wales life tables (2014–2016) in the cost-effectiveness model.[98] 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). Spline models were not explored for the mixture cure model approach as there is no established approach for incorporating these model types. Overall statistical fit of the mixture cure models was evaluated through the use of the Akaike information criterion (AIC) and Bayesian information criterion (BIC), as for the standard parametric survival models and flexible spline models.

As such, standard parametric survival models, flexible spline models and mixture cure models were explored for tisagenlecleucel and the blinatumomab and salvage chemotherapy comparators. 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.[99]

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:[94]

- AIC and BIC goodness-of-fit statistics (i.e. statistical fit)
- Visual inspection against the observed Kaplan-Meier curves
- Clinical plausibility for both short-term and long-term estimates of survival

It should be noted that to ensure that OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum (calculated using England and Wales life tables [2014–2016]). 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 were used directly from the pooled analysis of all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017) to model OS.[47-49]

The AIC and BIC values for the various standard parametric and spline models that were explored for the extrapolation of the pooled OS data for tisagenlecleucel are summarised in Table 29, and the extrapolations of OS using each model up to 10 years is presented in Figure 28 for all functions.

Table 29: Summary of goodness-of-fit data for tisagenlecleucel overall survival – standard parametric and spline models

Distribution	AIC	BIC
Exponential	623.60	626.86
Weibull	624.00	630.53
Gompertz	621.30	627.82
Lognormal	619.81	626.34
Log-logistic	621.88	628.40
Generalised gamma	621.68	631.46
Spline with single knot	621.85	631.64
Spline with two knots	623.83	636.88
Spline with three knots	625.84	642.16
Spline with four knots	627.84	647.41

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 28: Extrapolation of tisagenlecleucel overall survival – standard parametric and spline models

As demonstrated by Figure 28, none of the standard parametric models or flexible spline 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 only possible exception to this is the Gompertz model.

The AIC and BIC values together with the cure fraction rates for the various parametric functions explored for the extrapolation of the pooled OS data for tisagenlecleucel using the mixture cure model approach are summarised in Table 30. The extrapolations of OS using each model up to 10 years is presented in Figure 29.

Table 30: Summary of goodness-of-fit data for tisagenlecleucel overall survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	**621.34**	**627.87**	[redacted]
Weibull	623.11	632.90	[redacted]
Gompertz	623.29	633.07	[redacted]
Lognormal	621.68	631.47	[redacted]
Log-logistic	622.33	632.11	[redacted]
Generalised gamma	623.67	636.72	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 29: Extrapolation of tisagenlecleucel overall survival – mixture cure models

In contrast to the standard parametric and spline models, a number of the mixture cure models were seen to better reflect the plateau in the observed OS data and the expected continuation of this plateau in the longer-term. As previously described, 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 and spline models were seen to be unable to capture the observed plateau for tisagenlecleucel, the mixture cure models were considered most appropriate to consider for modelling 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 best-fitting mixture cure model by AIC and BIC was the exponential model, 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. Clinical plausibility of the cure fractions is an important consideration for selection of the base case mixture cure model. As previously noted, the NICE appraisal of blinatumomab in adult ALL patients (TA450) and the NICE mock appraisal of regenerative therapies performed by the York group both incorporated an assumption that patients still alive at a specified timepoint (4 years considered 'conservative' by the NICE Committee in TA450; 5 years in the NICE mock appraisal) were effectively cured and associated with general population mortality, which in the NICE mock appraisal was adjusted by a standardised mortality ratio for long-term ALL survivors.[44, 88] Feedback from UK clinical experts experienced in the treatment of r/r B-cell ALL in the paediatric and young adult setting was sought in the context of this submission, and this 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.[2] There is no reason to expect that a similar assumption would not hold for patients treated with tisagenlecleucel. Based on this collective evidence, and in the absence of long-term data to otherwise inform the assumed cure fraction, it is reasonable to take the proportion of patients still alive at 4 or 5 years in the observed tisagenlecleucel data as representative of the cured fraction. The pooled tisagenlecleucel clinical trial data provides follow-up to almost five years (54 months), at which point [redacted] of patients remain alive (the same percentage as alive at 48 months).[47-49] Based on this, the generalised gamma and lognormal mixture cure models were considered to produce implausibly low cure fractions ([redacted] and [redacted]); the implausibility of these cure fractions was validated by UK clinical experts.[2] The Weibull model resulted in a cure fraction slightly above the observed proportion of patients alive in the plateau of the observed data ([redacted]) and was therefore also dismissed as the base case. As the exponential distribution was the best-fitting and also estimated the cure fraction closest to a figure of [redacted], the exponential mixture cure model was therefore selected for the base case. The log-logistic and Gompertz models, which estimated lower cure fractions, were explored in scenario analyses (see Section B.3.8.3).

Salvage chemotherapy (FLA-IDA)

In the absence of any published OS data for salvage chemotherapy (FLA-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).[34, 99] 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, who stated that survival outcomes with the FLA-IDA regimen could be considered comparable to those observed with clofarabine monotherapy.

The AIC and BIC values for the various parametric and spline models that were explored for the extrapolation of the OS data for salvage chemotherapy (FLA-IDA) are summarised in Table 31 and the extrapolations of OS are presented in Figure 30 (for all functions up to 5 years) and Figure 31 (for the top-five fitting functions according to AIC over 2 years; to aid inspection of visual fit).

Table 31: Summary of goodness-of-fit data for salvage chemotherapy (FLA-IDA) overall survival – standard parametric and spline 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**
Spline with single knot	251.32	257.66
Spline with two knots	253.39	261.83
Spline with three knots	253.87	264.42
Spline with four knots	256.48	269.14

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 30: Extrapolation of salvage chemotherapy (FLA-IDA) overall survival – standard parametric and spline models

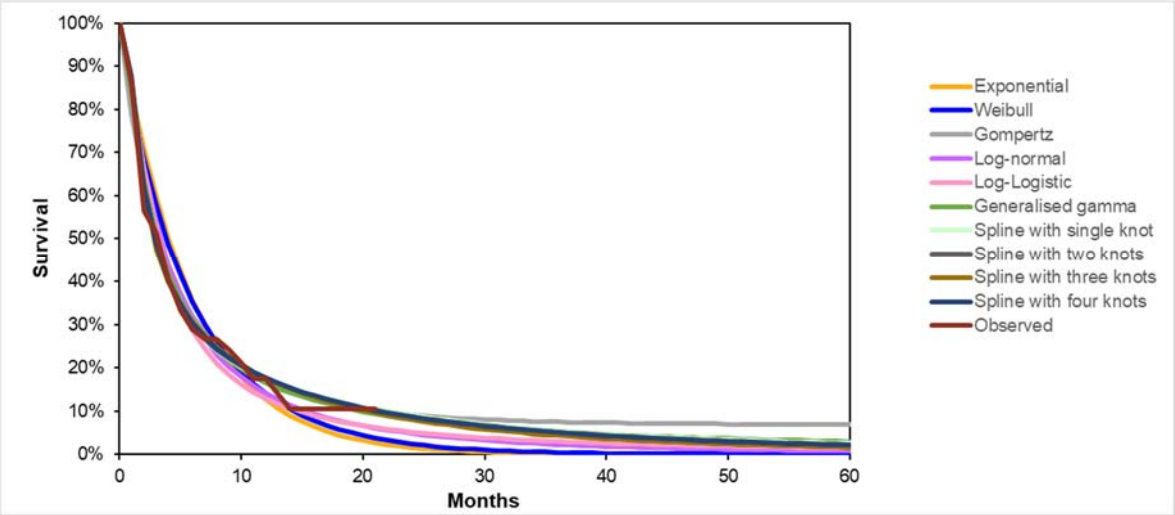
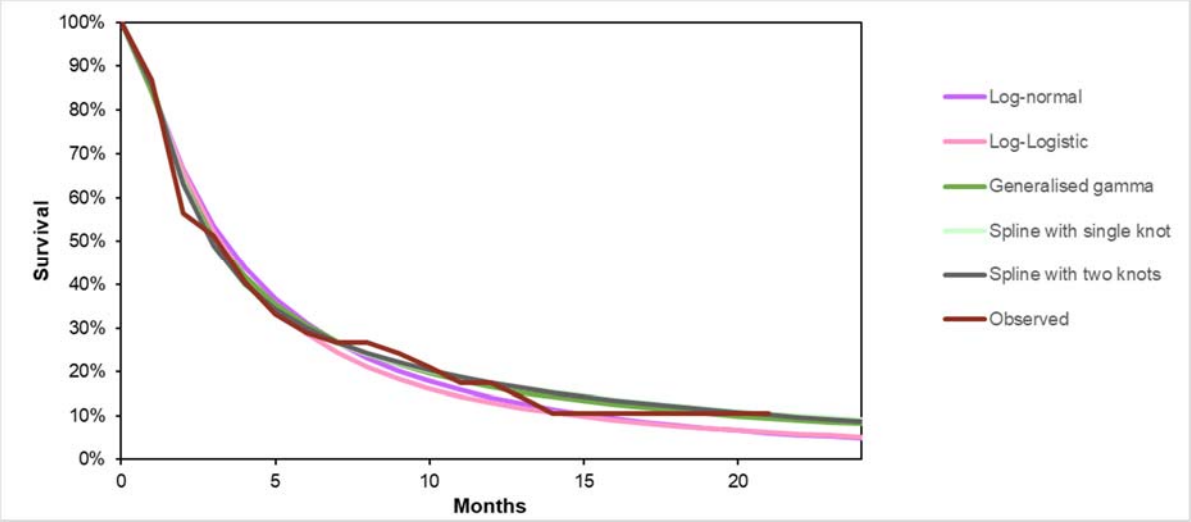


Figure 31: Extrapolation of salvage chemotherapy (FLA-IDA) overall survival – standard parametric and spline models (top five curves according to AIC)



For salvage chemotherapy (FLA-IDA), the spline with a single knot provided the best statistical fit to the Jeha *et al.* (2006) OS data in terms of AIC.[34] The log-logistic, lognormal, generalised gamma, spline single knot and spline two knots were the five 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 (Figure 31).

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 32. The extrapolations of OS using each model up to 5 years is presented in Figure 32.

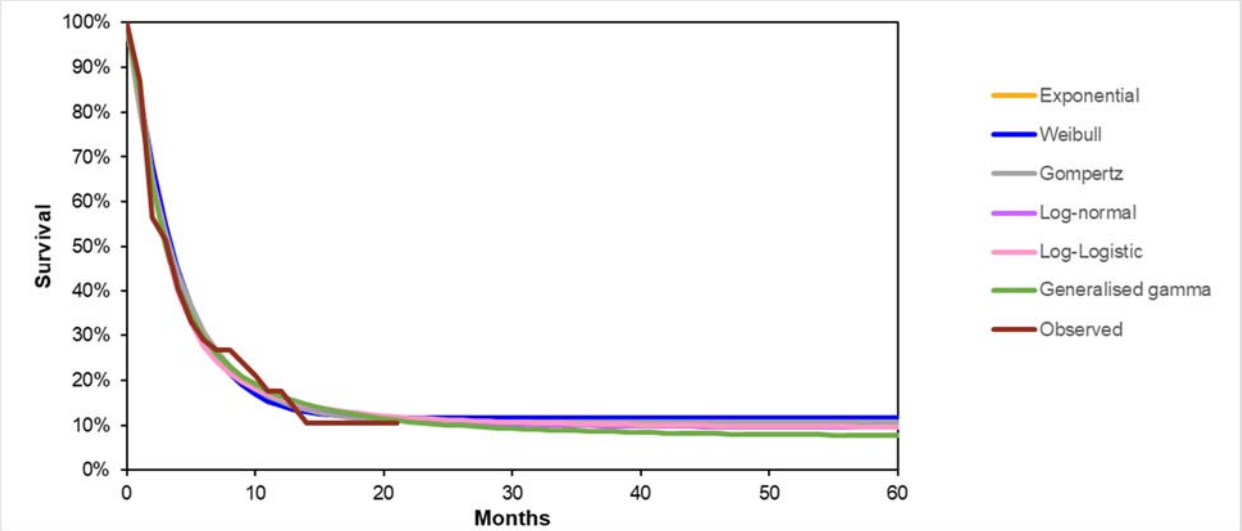
Table 32: Summary of goodness-of-fit data for salvage chemotherapy (FLA-IDA) overall survival – mixture cure models

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.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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



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 (FLA-IDA), the clinical plausibility of the survival estimates for the best fitting models amongst the standard parametric, spline model and mixture cure model approaches was considered. When considering survival in the long-term for the standard parametric models and spline models (i.e. not the mixture cure models), it was considered appropriate to adopt the same assumption as applied in TA450 in adult ALL patients and adopted for the NICE mock appraisal of regenerative therapies; namely, it was assumed that any patient still alive beyond a given time point (5 years) could be considered to be effectively cured and therefore associated with the same survival as that of the general population, adjusted by a SMR for long-term ALL survivors.[44, 84] The details of this approach are described in full later on in this section. The resultant estimates are presented in Table 33.

Table 33: Summary of survival projections for salvage chemotherapy (FLA-IDA) survival models

Timepoint	Proportion alive at specified timepoint					
	Generalised gamma	Spline single knot	Spline two knots	Mixture cure – lognormal	Mixture cure –	Mixture cure –

					log-logistic	generalised gamma
1 year	16.5%	17.5%	17.5%	15.9%	15.9%	16.4%
2 years	8.2%	9.1%	8.8%	10.9%	11.4%	10.3%
5 years	3.0%	2.6%	2.3%	9.5%	9.6%	7.7%
10 years	2.9%	2.5%	2.2%	9.4%	9.3%	7.3%

Abbreviations: FLA-IDA: fludarabine, cytarabine and idarubicin.

When presented to UK clinical experts, the feedback was that the three 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.[2, 34] Clinical expert feedback 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.[2] The mixture cure models predicted a long-term cured population of approximately (7.2%, 9.4%, 9.2%). Given that the only patients who would survive in the long-term when treated with salvage chemotherapy would be those who go on to receive allo-SCT, and only 16.39% of patients treated with salvage chemotherapy went on to allo-SCT in the Jeha *et al.* (2006) study, cure fractions of ~7-9% would imply that ~50% of patients treated with allo-SCT following salvage chemotherapy achieve successful treatment, post-transplant survival and hence cure.[34] This was considered too optimistic by UK clinical experts, and therefore the non-mixture cure models were preferred for the base case to model OS with salvage chemotherapy.[2] Of these, the generalised gamma parametric survival model was considered the most appropriate based on alignment with UK clinical expert feedback, predicting long-term survival of approximately 3% of patients, which was consistent with clinician estimates (see Table 33). [2]{{, #72}

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).[35, 99]

The AIC and BIC values for the various parametric and spline models that were explored for the extrapolation of the OS data for blinatumomab are summarised in Table 34, and the extrapolations of OS are presented in Figure 33 (for all functions up to 5 years) and Figure 34 (for the top-five fitting functions according to AIC over 2 years; to aid inspection of visual fit).

Table 34: Summary of goodness-of-fit data for blinatumomab overall survival – standard parametric and spline 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
Spline with single knot	340.09	346.84

Spline with two knots	342.18	351.17
Spline with three knots	343.79	355.03
Spline with four knots	345.75	359.24

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 33: Extrapolation of blinatumomab overall survival – standard parametric and spline models

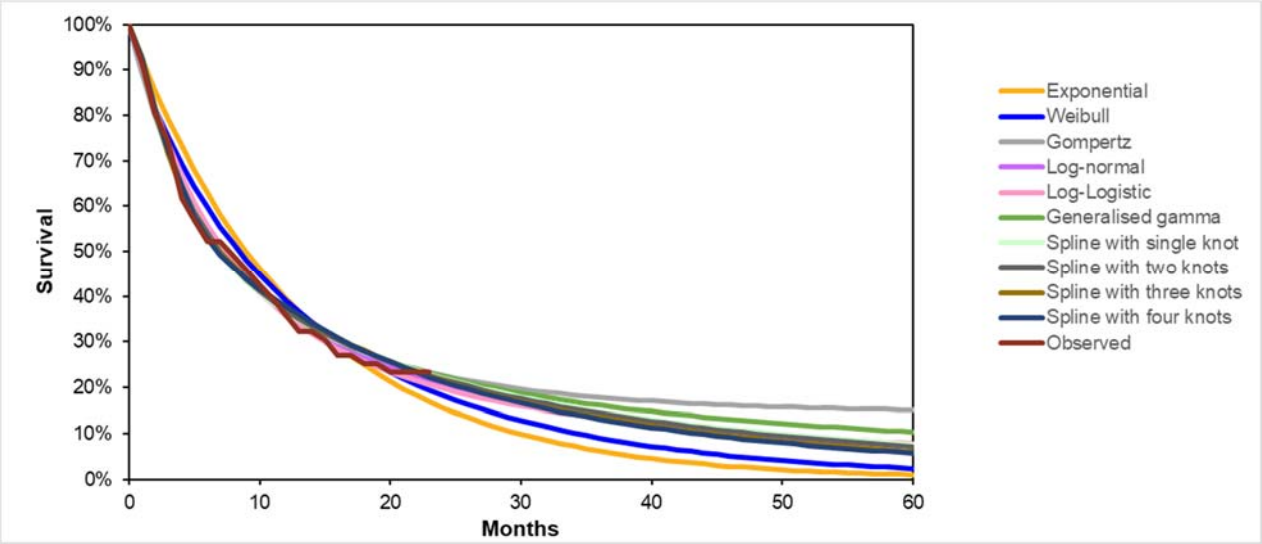
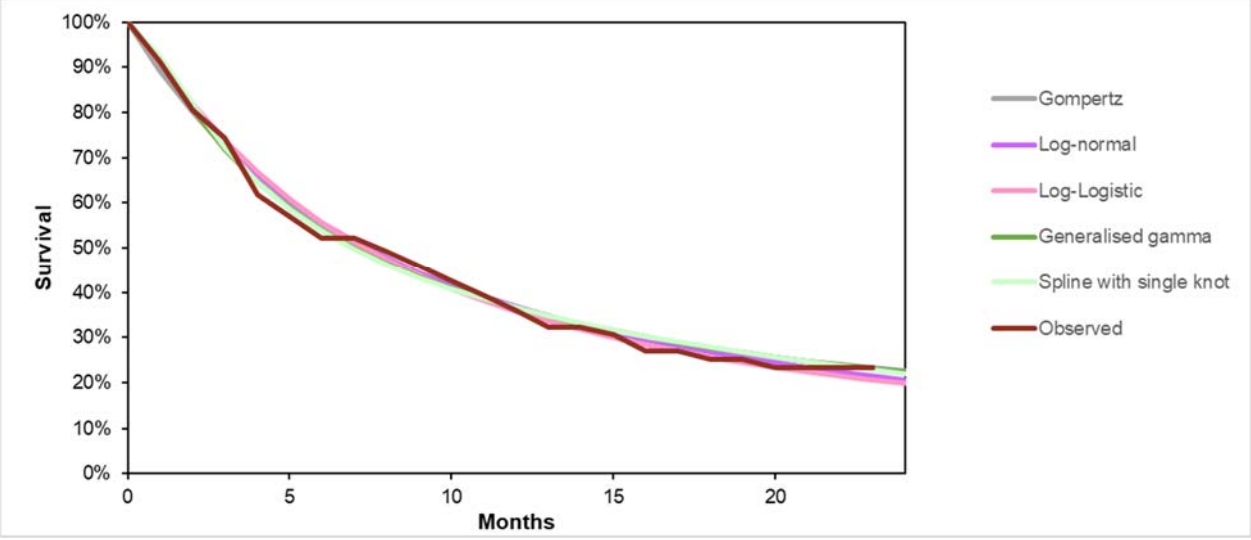


Figure 34: Extrapolation of blinatumomab overall survival – standard parametric and spline models (top five curves according to AIC)



For blinatumomab, the best-fitting curves by AIC and BIC were the Gompertz, lognormal, log-logistic, generalised gamma and spline with single knot. All five models provided a similar statistical and visual fit, with the lognormal function associated with the lowest AIC and BIC and a reasonable visual fit to the Kaplan-Meier data (see

Figure 34).[35] In the long-term, however, the choice of parametric distribution was seen to influence the survival projection relatively significantly with the Gompertz presenting the most optimistic extrapolation of the five best-fitting models.

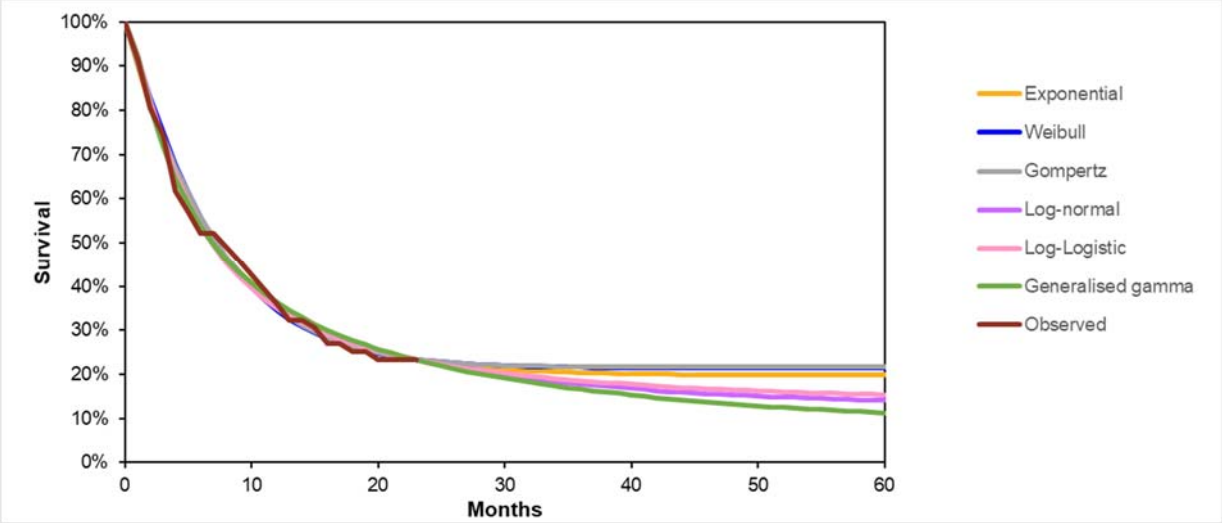
Mixture cure models were also explored for the blinatumomab OS profile. The AIC and BIC values together with the cure fraction rates for the various parametric functions explored for the mixture cure models are summarised in Table 35. The extrapolations of OS using each model up to 5 years are presented in Figure 35.

Table 35: 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.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 35: Extrapolation of blinatumomab overall survival – mixture cure models



The mixture cure models were associated with similar AIC values; BIC values varied a little more but were still within approximately 4 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).

The blinatumomab data is of limited follow-up (less than 24 months), meaning it is difficult to determine whether a true plateau exists in the data to support the existence of a 'cured' subpopulation and hence the use of a mixture cure model. The blinatumomab OS data indicates approximately 23% of patients alive at just before 24 months, though longer follow-up data would be required to ascertain whether this percentage would remain alive until longer follow-up times (e.g. the four or five years at which UK clinical experts suggest it can be assumed that patients who remain alive can be considered essentially cured).

The tisagenlecleucel OS data exhibited a short plateau at approximately 24 months, but this was seen to be only temporary with further drops in the Kaplan-Meier curve after 24 months before settling into an established plateau from approximately 39 months onwards. Given these considerations and the uncertainty associated with the long-term survival for patients treated with blinatumomab in this indication, it was considered overly optimistic to expect that the proportion of patients alive at the latest blinatumomab follow-up (approximately 23%) would remain alive in the long-term. This conclusion is supported by a comparison of the mean OS and undiscounted life

years associated with each of these mixture cure models when compared with the estimated mean OS and undiscounted life years when adopting an approach of a standard parametric model for blinatumomab, with all patients remaining alive at 5 years assumed to be effectively cured and associated with the same risk of death as the general population.

The latter approach reflects that applied in the NICE mock appraisal and in the NICE appraisal of blinatumomab in adult ALL (with uncertainty over the exact timepoint at which cure can be assumed), and therefore a reasonable reference point as to the estimated long-term survival profile for blinatumomab.{{, #92}}[84] The NICE mock appraisal adjusted general population mortality by an SMR to reflect the higher risk of death for ALL survivors compared to the general population, but for this validation comparison an SMR of 1 (i.e. no additional mortality beyond general population mortality) was assumed, in order to render the comparative approach an "optimistic" scenario.[84] The lognormal and Gompertz parametric functions were selected for this comparison, as these were two of the best-fitting standard parametric models and the Gompertz function represented the most optimistic of all standard parametric models in terms of survival projection. The resultant mean OS and undiscounted life years from this comparison are presented in Table 36.

Although the comparative approaches using a standard parametric model and general population mortality are themselves extrapolation approaches that are based on assumption and hence associated with uncertainty, in the absence of any long-term clinical data to provide a true source for validation, this exercise is considered informative. Table 36 demonstrates that even when employing "optimistic" versions of the comparison approaches (assuming an SMR of 1, using the most optimistic standard parametric model), the exponential, Weibull and Gompertz mixture cure models generate expected survival with blinatumomab that is considerably in excess of these. Based on this, the exponential, Weibull and Gompertz mixture cure models were excluded from further consideration on the basis of providing survival estimates that are highly unlikely to be observed in clinical practice.

Table 36: Assessment of the plausibility of the exponential, Weibull and Gompertz mixture cure models to model blinatumomab OS

	Lognormal parametric model with general population mortality (SMR of 1) assumed after 5 years	Gompertz parametric model with general population mortality (SMR of 1) assumed after 5 years	Cure model (exponential)	Cure model (Weibull)	Cure model (Gompertz)
Mean OS	71.4 months	134.1 months	170.1 months	182.9 months	185.1 months
Life years (undiscounted)	5.9 years	11.1 years	14.1 years	15.2 years	15.3 years

Abbreviations: OS: overall survival; SMR: standardised mortality ratio.

Conversely, the generalised gamma mixture cure model was associated with a cure fraction of only 3.9%, which was considered unrealistically low. Therefore, the lognormal and loglogistic mixture cure models were taken forwards for consideration against the best-fitting standard parametric models.

The five best-fitting standard parametric or spline models were considered alongside the mixture cure lognormal and mixture cure log-logistic models in terms of the clinical plausibility of their long-term projections in order to decide upon the model choice for the base case analysis. As for salvage chemotherapy (FLA-IDA) discussed above, where standard parametric or spline models (i.e. not the mixture cure models) were considered, it was assumed that any patient still alive beyond a given time point (5 years) could be considered to be effectively cured and therefore associated with the same survival as that of the general population, adjusted by a SMR for long-term ALL survivors.[44, 84] The long-term survival estimates predicted by each of the approaches considered are provided in Table 37.

Table 37: Summary of OS projections for blinatumomab survival models

Timepoint	Proportion alive at specified timepoint						
	Gompertz	Log-logistic	Lognormal	Generalised gamma	Spline with single knot	Mixture cure – lognormal	Mixture cure – loglogistic
1 year	36.7%	35.8%	36.7%	36.5%	36.6%	35.8%	35.1%
2 years	22.6%	19.8%	20.6%	22.4%	22.0%	22.7%	22.8%
5 years	15.1%	7.8%	7.3%	10.3%	7.6%	14.1%	15.4%
10 years	14.9%	7.7%	7.2%	10.1%	7.5%	12.1%	13.4%

Abbreviations: OS: overall survival.

Clinical expert feedback was that blinatumomab does not represent a curative therapy. However, allo-SCT is curative and so 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, 34.29% 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. Long-term estimates for treatment with blinatumomab against which to validate these long-term extrapolations are unavailable. However, in the adult study of blinatumomab presented in TA450, a Gompertz function was selected as the most appropriate function. The shape of the survival projection resulting from the Gompertz curve selection in TA450 was most closely resembled by either the Gompertz standard parametric model or the two mixture cure models: these three options were associated with similar survival projections, as reported in Table 37. Given the use of subsequent allo-SCT in a proportion of patients provides the potential for a cure, and the fact that a mixture cure model was utilised in the base case for tisagenlecleucel, it was decided to use one of the mixture cure models for blinatumomab efficacy rather than the Gompertz function. The mixture cure model chosen for the base case was the mixture cure lognormal, on the basis that having slightly better statistical fit by AIC and BIC than the log-logistic mixture cure model.

Summary of base case extrapolations (OS)

Figure 36 presents the base case OS extrapolations for tisagenlecleucel (mixture cure - exponential), salvage chemotherapy (generalised gamma, with patients alive at 5 years assumed to be effectively cured) and blinatumomab (mixture cure – lognormal).

Figure 36: Base case OS extrapolations

Extrapolation of OS – assumption of a cure timepoint with standard parametric models

Although the base case models for OS for tisagenlecleucel and blinatumomab were mixture cure models, the base case for salvage chemotherapy (FLA-IDA) was a standard parametric survival model. Furthermore, a number of scenario analyses explored the use of standard parametric models. Where such models were used, these models were not extrapolated in an unadjusted manner over the entire time horizon, but were instead only extrapolated up to a specified timepoint, after which patients who remained alive in the model were subject to only general population mortality, adjusted by a SMR for long-term ALL survivors. This reflects an assumption that any ALL patient who remains alive beyond a certain timepoint can be considered to be effectively 'cured'. The precedent for this assumption has been established in ALL both in TA450 and in the NICE mock appraisal of regenerative therapies, and was confirmed by expert clinical feedback to inform this submission.[44, 84] Incorporation of this assumption represents an alternative approach to that of mixture cure models for assuming that a proportion of the population achieve a definitive cure. Where mixture cure models were seen to be inappropriate due to poor fit or implausible long-term survival estimates (e.g. for salvage chemotherapy [FLA-IDA]), this alternative approach was therefore utilised. In addition, given the precedent established for this approach, scenario analyses were also conducted considering the modelling of all therapies in this manner.

Where this approach was used, the timepoint at which the "cure" was assumed was 5 years (this timepoint was explored in scenario analyses). Survival for patients alive in the model beyond this point was modelled using England and Wales life tables (2014–2016), with a mortality adjustment for 5-year ALL survivors using a SMR adjustment derived from the literature. The same mortality risk was applied to all treatments. 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.[100-103] MacArthur *et al.* (2007) was used in the base case in line with the source used in the NICE mock appraisal.[84, 100] Whilst it is difficult to validate the SMR, this SMR was considered appropriate by UK clinical experts. The SMR inputs from the three other studies were evaluated in scenario analyses.[101-103] These SMR input sources are summarised in Table 38.

Table 38: Long-term survival input sources

Publication	Population	Sample Size	SMR Measure

Base case			
MacArthur 2007[100]	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**
Scenario analyses			
Armstrong 2016[101]	All childhood cancer survivors diagnosed with cancer before age 21 (paediatric and adolescent) and alive at least 5 years after diagnosis	Overall sample size: 34,033; Sample size for ALL patients: 8,500	SMR for ALL 5-year survivors: **15.2**
Bhatia 2005[103]	Paediatric, adolescent, and adult patients who survived two or more years after autologous allo-SCT for hematologic malignancies	Overall sample size: 854; Sample size for ALL patients: 59	SMRs for ALL: Years 2–5: **1004** Years 6–10: **26.5**; 11 or more years: **4.2**
Socié 1999[102]	Paediatric, adolescent, and adult patients who received allogenic allo-SCT between 1980 to 1993 and were disease-free 2 years post procedure; 22% of patients were diagnosed with ALL, and among those, 45% received allo-SCT in CR1, 45% in CR2, and 10% not in remission	Overall sample size: 6,691; Sample size for ALL patients: 1,458	Relative mortality rate for ALL patients vs. general population: Years 2–5: **20.1** Years 5–9: **25.9**; 10 or more years: **15.1**

Abbreviations: ALL, acute lymphoblastic leukaemia; CR1, first complete remission; CR2, second complete remission; allo-SCT, haematopoietic stem cell transplant; SMR, standardised mortality ratio.
Source: Armstrong *et al.* (2016);[101] Bhatia *et al.* (2005);[103] MacArthur *et al.* (2007);[100] Socié *et al.* (1999).[102]

Event-free survival

Tisagenlecleucel

For tisagenlecleucel, the EFS IPD was used directly from the pooled analysis of all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017) to model OS.[47-49] Consistent with the approach used to extrapolate OS, standard parametric models, flexible spline models and mixture cure models were considered for extrapolation of the EFS data beyond the observed trial period.

The AIC and BIC values for the various parametric and spline models that were explored for the extrapolation of the pooled EFS data for tisagenlecleucel are summarised in Table 39, and the extrapolations of EFS using these models are presented in Figure 37 (for all functions up to 10 years).

Table 39: Summary of goodness-of-fit data for tisagenlecleucel event-free survival – standard parametric and spline models

Distribution	AIC	BIC
Exponential	672.38	675.64
Weibull	598.46	604.98
Gompertz	635.91	642.43
Lognormal	602.07	608.59
Log-logistic	600.16	606.69
Generalised gamma	600.31	610.10
Spline with single knot	599.33	609.12
Spline with two knots	599.55	612.60

A smaller AIC or BIC value represents a better goodness of fit. AIC/BIC values are not available for the spline with three/four knot functions as these did not converge.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 37: Extrapolation of tisagenlecleucel event-free survival – standard parametric and spline models

None of the standard parametric or flexible spline 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.

The AIC and BIC values of the mixture cure models are summarised in Table 40. The extrapolations of EFS up to 10 years using these mixture cure models are provided in Figure 38.

Table 40: Summary of goodness-of-fit data for tisagenlecleucel event-free survival – mixture cure models

Distribution	AIC	BIC	Cure rate (%)
Exponential	638.69	645.21	[redacted]
Weibull	600.46	610.25	[redacted]
Gompertz	636.69	646.47	[redacted]
Lognormal	604.07	613.86	[redacted]
Log-logistic	602.17	611.96	[redacted]
Generalised gamma	**600.59**	**613.64**	[redacted]

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 38: Extrapolation of tisagenlecleucel event-free survival – mixture cure models

The best-fitting mixture cure models by AIC and BIC were the Weibull, generalised gamma and log-logistic models. The various models were seen to produce a wide range in the estimated cure fraction (from [redacted] to [redacted]). The cure fractions estimated by the Weibull and log-logistic models were considered implausible based on the evidence of a plateau effect at approximately 40% of patients having not experienced the EFS event and in terms of consistency with the cure fraction estimated in the base case mixture cure model for OS ([redacted]). In contrast, the generalised gamma mixture cure model was seen to capture the plateau in the observed tisagenlecleucel data and provided a cure fraction not too dissimilar to that in the mixture cure model for OS. The generalised gamma mixture cure model was therefore selected as the base case model for tisagenlecleucel EFS.

Salvage chemotherapy (FLA-IDA)

EFS data were not available for salvage chemotherapy (FLA-IDA) from the Jeha *et al.* (2006) study.[34] As such, the EFS curves were derived from the available OS curves, consistent with the approach taken in the NICE mock appraisal.[84] Up to 5 years, 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.[104] 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 identified in the literature that reported both OS and EFS. Only one other study of the 19 identified in the clinical SLR as being in similar patient populations to the tisagenlecleucel clinical trials reported both OS and EFS data; however, this study investigated bortezomib, which was not considered to have similar outcomes to salvage chemotherapy.[105] 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.[106] 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. After Year 5, the cumulative survival probabilities of EFS were assumed to flatten up until they reached OS, based on the assumption that if patients still alive at this timepoint are effectively "cured" then they would not be expected to experience an EFS event other than the death event due to SMR-adjusted natural mortality represented by the OS curve. Given the generalised gamma function was chosen in the base case analysis to model the long-term

extrapolation of OS, the cumulative HR was applied to this extrapolation to derive the EFS curve for salvage chemotherapy (FLA-IDA) in the base case (see Figure 39).

Blinatumomab

For blinatumomab, EFS data were also not available from the von Stackelberg *et al.* (2016) study and therefore, the same cumulative HR approach as used for salvage chemotherapy (FLA-IDA) was adopted.

The von Stackelberg *et al.* (2016) study did provide Kaplan-Meier RFS data, which was defined as the time from CR to the first relapse, evaluated for the 27 patients who achieved a CR at Week 12.[35] In order to try and use the RFS data from the trial, a scenario analysis was conducted in which parametric models were used to extrapolate the RFS data beyond the observed trial period for those achieveing remission. Prior to Week 12, it was assumed that the estimate of blinatumomab EFS matched that of the blinatumomab OS curve.

Base case extrapolations (EFS)

Figure 39 presents the base case EFS extrapolations for tisagenlecleucel (mixture cure – generalised gamma), salvage chemotherapy (cumulative HR based on generalised gamma for OS) and blinatumomab (cumulative HR based on mixture cure – lognormal for OS).

Figure 39: 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 pooled analysis of patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=[redacted]) in all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017 data cut-off). For blinatumomab, AE rates were derived from von Stackelberg *et al.* (2016) and for salvage chemotherapy (FLA-IDA), in the absence of any clinical evidence for FLA-IDA, the AE rates from Jeha *et al.* (2006) were used.[34, 35] 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, who agreed that no AEs with either a substantial cost or substantial effect on patient quality of life had been omitted from the analysis.[2]

Table 41: Incidence of Grade 3 or 4 adverse events included in the model

AEs	Tisagenlecleucel	Salvage chemotherapy (FLA-IDA)	Blinatumomab
Source for AE rates	**Pooled analysis[a] (ELIANA, ENSIGN and B2101J)[47-49]**	**Jeha *et al.* (2006)[34,b]**	**von Stackelberg *et al.* (2016)[35,c]**
Acute kidney injury	[redacted]	-	-
Alanine aminotransferase increased	[redacted]	-	15.71%
Anaemia	[redacted]	-	35.71%
Anorexia	[redacted]	19.67%	-
Aspartate aminotransferase increased	[redacted]	-	11.43%
Bacteraemia	-	13.11%	-
Blood bilirubin increased	[redacted]	-	-
Capillary leak syndrome	[redacted]	-	-
Cytokine-release syndrome	[redacted]	-	5.71%
Decreased appetite	[redacted]	-	-
Dermatitis	-	11.48%	-
Diarrhoea	-	13.11%	-
Encephalopathy	[redacted]	-	-
Epistaxis	-	13.11%	-
Febrile neutropenia	[redacted]	49.18%	17.14%
Hallucination	-	13.11%	-
Haemoglobin	[redacted]	-	-
Hepatomegaly	-	11.48%	-
Hypertension	-	9.84%	5.71%
Hypocalcaemia	[redacted]	-	-
Hypokalaemia	[redacted]	-	17.14%
Hypophosphataemia	[redacted]	-	-
Hypotension	[redacted]	18.03%	-
Hypoxia	[redacted]	-	-
Leukopenia	[redacted]	-	10.00%
Lymphocyte count decreased	[redacted]	-	-
Nausea	[redacted]	16.39%	-
Neutropenia	[redacted]	14.75%	17.14%
Neutrophil count decreased	[redacted]	-	12.86%
Petechiae	-	11.48%	-
Platelet count decreased	[redacted]	-	14.29%
Pleural effusion	-	9.84%	-
Pneumonia	-	9.84%	-
Pulmonary oedema	[redacted]	-	-

Pyrexia	[redacted]	14.75%	14.29%
Respiratory distress	-	11.48%	-
Sepsis	-	13.11%	-
Staphylococcal bacteraemia	-	9.84%	-
Thrombocytopenia	[redacted]	-	21.43%
White blood cell count decreased	[redacted]	-	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 cost.
[a]Pooled analysis of ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017), B2101J (30th Jan 2017 data cut-off). Based on grade 3 or 4 AEs, regardless of study drug relationship, occurring any time post tisagenlecleucel infusion in >5% patients.
[b]Jeha *et al.* (2016). Based on grade ≥3 AEs, regardless of causality that occurred in ≥10% of patients in all cycles.[34]
[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 (31st Dec 2017), ENSIGN (6th Oct 2017), B2101J (30th Jan 2017);[47-49] Jeha *et al.* (2006);[34] von Stackelberg *et al.* (2016).[35]

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 the value sets for converting EQ-5D-Y to a utility score are still under development, the utility scores were derived based on the EQ-5D-3L data only.[107] 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 generated using patient-level EQ-5D-3L data from the ELIANA trial (31st Dec 2017) were calculated by the following categories, corresponding to the model health states; including:[47]

- **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[63]
- **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.[108] 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 42.

Table 42: Descriptive statistics on EQ-5D utility values in ELIANA trial

Health States	N patients[a]	N assessments	Mean	SD
EFS	[redacted]	[redacted]	[redacted]	[redacted]
Before treatment/post-EFS	[redacted]	[redacted]	[redacted]	[redacted]

[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; SD: standard deviation.
Source: ELIANA CSR (31st Dec 2017).[47]

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 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.

The SLR identified 580 records and 19 were obtained for full text review. Ultimately, no studies were identified that met the pre-specified inclusion criteria. Consequently, a targeted literature review was conducted and two utility studies were identified as being potentially relevant to the decision problem.[109, 110]

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.[109] 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. Given the very limited sample size available for EQ-5D data from the ELIANA trial, these utility values 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.

Sung *et al.* (2003) reported physician elicited utility estimates for acute myeloid leukaemia patients who survived post transplantation without recurrent disease.[110] Estimates of disutility associated with chemotherapy and transplantation were reported in this study and were subsequently used within the economic analysis.

B.3.4.4 Adverse reactions

Inputs for treatment disutility included within the economic analysis were based on estimates from the study by Sung *et al.* (2003).[110] 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 (FLA-IDA) or 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, 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.[2] For blinatumomab, this approach fits

less well with the fact that patients may be likely to experience AEs (albeit to a lesser degree) throughout the treatment period; as such, this assumption was explored in a scenario analysis, where the utility decrement for treatment with blinatumomab was removed, however this was found to have very little impact on the ICER (see Section B.3.8.3).

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.[84] The rates of subsequent allo-SCT were obtained from the same clinical trial studies used for the efficacy estimation.[34, 35, 47-49] Both of the above estimates are assumed to capture the utility decrements for all short-term AEs associated with treatment, with the exception for the CRS.

Additional treatment disutilities were considered for patients experiencing grade 3 or 4 CRS. The CRS rate for tisagenlecleucel was derived from the pooled analysis of all three tisagenlecleucel clinical trials and the rate for blinatumomab was derived from von Stackelberg *et al.* 2016.[35, 47] 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 (31st Dec 2017; hospitalisation data were not collected in the ENSIGN or B2101J trials).[47] 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 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

Because the utility input 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 calculated based on Janssen *et al.* (2014), which described the health utilities of healthy populations by different age groups using the EQ-5D index population norms based on the UK time-trade-off value sets.[72]

Utility values used within the economic model

A summary of the utility values used within the economic model is provided in Table 43.
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)[109] were used in the base case economic analysis. It is acknowledged that there are some limitations with use of the utility values from Kelly *et al.* (2015); most notably that this means the HRQoL data were not collected directly from the population of the tisagenlecluecel 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. In light of the limited sample size of the ELIANA EQ-5D data and the fact that no other more relevant sources for utility values were identified by the SLR, the values from Kelly *et al.* (2015) were considered most appropriate for the base case 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 43: 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 (SD 0.16)	N/A	N/A	Kelly *et al.* (2015)[109]
PD	0.75 (SD 0.02)	N/A		
Long-term survival	0.91 (SD 0.16)	N/A		
Health state utility values (scenario analysis)				
EFS	0.80 (SD 0.03)	N/A	N/A	ELIANA (31st Dec 2017)[47]
PD	0.63 (SD 0.06)	N/A		
Treatment disutility				
Tisagenlecleucel	-0.42	25.85	N/A	Sung *et al.* (2003)[110]
Salvage chemotherapy (FLA-IDA)	-0.42	21		
Blinatumomab	-0.42	9.24		
Grade 3 or 4 CRS (ICU stay)				
Tisagenlecleucel	-0.91	[redacted]	[redacted]	ELIANA (31st Dec 2017)[57]
Blinatumomab	-0.91	11.1	5.71%	ELIANA (31st Dec 2017), von Stackelberg *et al.* (2016) (% of patients)[35, 47]
ICU stay not due to CRS				
Tisagenlecleucel	-0.91	[redacted]	N/A	ELIANA (25th Apr 2017)[47]
Subsequent allo-SCT disutility				
Tisagenlecleucel	-0.57	[redacted]	[redacted]	Pooled tisagenlecleucel clinical trials (ELIANA [31st Dec 2017]; ENSIGN [6th Oct 2017]; B2101J [30th Jan 2017])[47-49]
Salvage chemotherapy (FLA-IDA)	-0.57	365	16.39%	Jeha *et al.* (2006)[34]
Blinatumomab	-0.57	365	34.29%	von Stackelberg *et al.* (2016)[35]
Age-related utilities				
Age <25	0.94	N/A	N/A	Janssen *et al.* (2014)[72]
Age 25-34	0.93			
Age 35-44	0.91			
Age 45-54	0.85			
Age 55-64	0.80			
Age 65-74	0.78			
Age 75+	0.73			

Abbreviations: CRS: cytokine-release syndrome; EFS: event-free survival; allo-SCT: haematopoietic stem cell transplantation; ICU: intensive care unit; N/A: not applicable; PD: progressive disease.

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

An SLR was conducted 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.

The SLR identified 671 publications of which 29 were selected for full text review. Only three publications were ultimately considered to be relevant to patients aged up to 25 with r/r B-cell ALL that reported healthcare resource utilisation and associated cost data (Maziarz *et al.* [2015], Lehne *et al.* [2016] and Maziarz *et al.* [2016]).[111-113] Full details of these studies are presented in Appendix I.

The included full-text publication (Maziarz *et al.* [2016]) and conference abstract (Maziarz *et al.* [2015]) were both based on the same study that assessed five-year healthcare costs and resource use using claim data from the IMS LifeLink PharMetrics Plus™ and the Truven Health MarketScan® in the US and was based on 209 paediatric patients (mean age: 9.8 years; SD: 4.8) with a diagnosis of ALL.[111, 112] The second study by Lehne *et al.* (2016) assessed the costs from the perspective of the German statutory health insurance (i.e. from a payers' perspective) using the German Health Risk Institute database and was based on 30 paediatric patients (mean age: 9.3 years; SD: 5.3) with a diagnosis of ALL.[113]

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. Given both of the above identified studies were not conducted from a UK NHS or PSS perspective, neither study was used to inform the economic analysis. Appropriate sources of unit costs, such as NHS reference costs 2016–17, the British National Formulary (BNF) and the electronic Marketing Information Tool (eMIT) were used for cost inputs in the model.[114-116] Resource use estimates were based on a number of sources including data from the ELIANA clinical trial (31st Dec 2017; given this was the only tisagenlecleucel trial to collect resource use and hospitalisation data), 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.[2, 44, 47, 81]

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.

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.[2] The impact on caregivers, whether they be formal caregivers or informal caregivers (e.g. family members) is not considered in the analysis. If the impact of pALL on caregivers were to also be incorporated, this 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

Pre-treatment costs

As described in Section B.3.2.3, there are three pre-treatment phases that patients undergo prior to receiving infusion with tisagenlecleucel: leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy. 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

The cost of leukapheresis was estimated to be £1,020 based on NHS Reference Costs 2016-2017 (Elective Inpatient, SA43Z Leucopheresis).[114] 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

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 in all three trials.[47-49] As such, the cost of bridging chemotherapy was based on feedback from UK clinical experts, who stated that patients would typically receive bridging chemotherapy in the outpatient setting.[2] 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 [redacted]. Given the manufacturing time of tisagenlecleucel may reduce even further as the manufacturing process is refined, in clinical practice, patients may receive bridging chemotherapy for a shorter duration of time than is estimated in the base case economic analysis.

- Allopurinol 100 mg/m^2 orally three times daily for 5 days
- Dexamethasone 6 mg/m^2/day for 14 days then dexamethasone 3 mg/m^2/day for 7 days
- Vincristine 1.5 mg/m^2 iv weekly for 3 weeks
- Intrathecal methotrexate 12 mg on days 1 and 8
- Co-trimoxazole 480 mg orally twice daily for two consecutive days each week for 3 weeks

Drug costs for the above regimens were obtained from eMIT and BNF 2018.[115, 116] The average dose required per administration was based on an average BSA of [redacted] (based on the ELIANA [31st Dec 2017] and ENSIGN [6th Oct 2017) trials; height IPD were not available for the B2101J study).[47, 48] 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 3-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 2016–2017: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (for the first administration) and NHS Reference Costs 2016–2017: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (for subsequent administrations).[114]

The proportion of patients who received infusion with tisagenlecleucel that were assumed to receive bridging chemotherapy was [redacted] based on pooled data from ELIANA (25th Apr 2017) and ENSIGN (6th Oct 2017) (data from the latest ELIANA cut-off or B2101J were not available). 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

As stated in the draft 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.[1] 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 draft SmPC and the cost of receiving each regimen was included within the economic model.[1]

- 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); 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.*

It was assumed that [redacted] of patients who received infusion with tisagenlecleucel received lymphodepleting chemotherapy based on pooled data from all three tisagenlecleucel clinical trials: ELIANA (25th Apr 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017).[50] 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 (25th Apr 2017), within which [redacted] of patients received Regimen 1 and [redacted] of patients received Regimen 2.[50] These percentages were scaled up to 100% (i.e. [redacted] of patients were assumed to receive Regimen 1 and [redacted] of patients were assumed to receive Regimen 2) within the economic model.

Drug costs for the above regimens were obtained from eMIT.[115] The average dose required per administration was based on an average BSA of [redacted] (based on the ELIANA [31st Dec 2017] and ENSIGN [6th Oct 2017) trials; height IPD were not available for the B2101J study).[47, 48] 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 (25th Apr 2017) where [redacted] of patients were associated with a length of hospitalisation stay of [redacted] days.[50] The average daily cost of hospitalisation was based on NHS Reference Costs 2016–2017 and the weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more (PM40A, PM40B, PM40C).[114] This is a conservative estimate given the consensus amongst UK clinical experts contacted 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.[2] This alternative assumption was explored within a scenario analysis.

The remaining [redacted] 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 2016–2017: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (for the first administration) and NHS Reference Costs 2016–2017: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (for subsequent administrations).[114] 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 pre-treatment costs for tisagenlecleucel is provided below.

Table 44: 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 administration	Total number of infusions/ packs required	Drug cost per regimen (£)	Proportion receiving regimen	Total cost (£)	Source/Assumptions
Leukapheresis								**£1,020.08**	
Bridging chemotherapy (drug costs)								**£85.10**	
Allopurinol	100 mg/m^2 orally three times daily for five days	£0.27 (28 x 100 mg tablets)	127.25	1	1	£0.27	N/A	£0.27	eMIT 2017 (NPC Code: DJA084 Allopurinol 100 mg tablets/packsize 28)[35]
Dexamethasone	6 mg/m^2 orally for 14 days then tapered for seven days (assumed to receive three mg/m^2 daily during tapering)	£14.46 (50 x 2 mg tablets)	6.36	1	2	£28.92	N/A	£28.92	eMIT 2017 (NPC Code: DFN018 Dexamethasone 2 mg tablets/packsize 50)[35]
Vincristine	1.5 mg/m^2 IV weekly for three weeks	£5.32 (2 mg vial)	1.91	1	3	£15.95	N/A	£26.60	eMIT 2017 (NPC Code: DHA111 Vincristine 2 mg/2 ml solution for injection vials/packsize 5)[35]
Intrathecal methotrexate	12 mg intrathecally on days one and eight	£6.44 (5 mg vial)	12.00	3	6	£38.63	N/A	£57.96	eMIT 2017 (NPC Code: DHA038 Methotrexate 5 mg/2 ml solution for injection vials/packsize 5)[35]
Co-trimoxazole	480 mg orally twice daily on two	£1.33 (28 x 480	480.00	1	1	£1.33	N/A	£1.33	eMIT 2017 (NPC Code: DEA224 Co-trimoxazole 80

	consecutive days each week	mg tablets)							mg/400 mg tablets/packsize 28)[35]
Lymphodepleting chemotherapy								**£122.46**	
Regimen 1 (drug costs)									
Fludarabine	30 mg/m^2 iv daily for four doses	£23.01 (50 mg vial)	38.17	1	4	£123.82	[redacted]	£122.10	eMIT 2017 (NPC Code: DHA377 Fludarabine phosphate 50 mg/2 ml solution for injection)[35]
Cyclophosphamide	500 mg/m^2 iv daily for two doses	£15.89 (1000 mg vial)	636.24	1	2				eMIT 2017 (NPC Code: DHA014 Cyclophosphamide 1 g powder for solution for injection)[35]
Regimen 2 (drug costs)									
Cytarabine	500 mg/m^2 iv daily for two days	£6.13 (1000 mg vial)	636.24	1	2	£26.06	[redacted]	£0.36	eMIT 2017 (NPC Code: DHA020 Cytarabine 1 g/10 ml solution for injection)[35]
Etoposide	150 mg/m^2 iv daily for three days	£2.30 (100 mg vial)	190.87	2	3				eMIT 2017 (NPC Code: DHA320 Etoposide 100 mg/5 ml solution for injection)[35]

Note: The average dose required per administration is based on an average BSA of 1.27 m^2 (based on the ELIANA [31st Dec 2017 data cut-off] and ENSIGN [6th Oct 2017 data cut-off) trials). Some unit costs are rounded to 2dp.
Abbreviations: eMIT: electronic market information tool; iv: intravenous; mg: milligrams.

Table 45: 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)					**£986.07**	
Vincristine (see dose above in Table 44)	3	£596.62	N/A	100%	£596.62	• Outpatient administration costs based on NHS Reference Costs 2016–2017: Chemotherapy, SB12Z Outpatient, Deliver Simple Parenteral Chemotherapy at First Attendance (£173.99; for the first administration) and NHS Reference Costs 2016-2017: Chemotherapy, SB15Z, Outpatient, Deliver Subsequent Elements of a Chemotherapy Cycle (£205.09 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[34] • The proportion of patients receiving lymphodepleting chemotherapy in the outpatient setting was based on data from the ELIANA clinical trial (25th Apr 2017)[117]
Intrathecal methotrexate (see dose above in Table 44)	2	£389.45	N/A	100%	£389.45	
Lymphodepleting chemotherapy (outpatient administration costs)					**£269.04**	
Regimen 1 (see dose above in Table 44)	4	£789.27	[redacted]	[redacted]	£266.26	
Regimen 2 (see dose above in Table 44)	3	£584.18	[redacted]		£2.78	

Abbreviations: NHS: National Health Service.

Table 46: 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)	£772.11	13.98	£10,794.09	[redacted]	**£7,101.38**	• The proportion of patients receiving lymphodepleting chemotherapy administration in hospital was based on data from the ELIANA clinical trial (25th Apr 2017); hospitalisation resource use data were not collected in ENSIGN or B2101J)[117]

						• The average daily cost of hospitalisation was based on NHS Reference Costs 2016–2017 and the weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with length of stay one day or more (PM40A, PM40B, PM40C).[34]

Abbreviations: NHS: National Health Service.

Tisagenlecleucel infusion costs

The costs associated with the infusion of tisagenlecleucel within the economic model included the acquisition cost of tisagenlecleucel, which includes transportation, manufacture and delivery, and the associated hospitalisation (including ICU) and outpatient administration costs (see Table 47). 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 draft Summary of Product Characteristics in Appendix C):[1]

- 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), [redacted] 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.[50] As such 100% of patients were assumed to incur an average length of hospitalisation stay of [redacted] days (based on data from the ELIANA trial [25th Apr 2017]), the cost of which was based on NHS Reference Costs 2016-2017 (Weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more PM40A–PM40C) (see Table 47).[50, 114] It can be considered that the assumption of [redacted] 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.[2]

Finally, it was also assumed, based on data from the ELIANA trial (25th Apr 2017), that on average, patients receiving infusion with tisagenlecleucel would spend [redacted] days in ICU (not due to CRS) following infusion.[50] 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. The average daily cost of ICU was estimated to be £1,559.68 based on NHS Reference Costs 2016–2017 and a weighted average of: Paediatric Critical Care [excluding transportation] XB01Z–XB07Z, XB09Z (see Table 47).[114] Based on feedback from UK clinical experts, the assumption of [redacted] days of ICU stay (not due to CRS) may be considered a conservative estimate because in clinical practice, the feedback was that clinicians would be unlikely to treat a patient in ICU for reasons other than CRS.[2]

Table 47: Infusion costs (and other hospitalisation costs) with tisagenlecleucel

Cost of infusion	Input	Source / Assumptions
Tisagenlecleucel infusion acquisition cost	£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	94.7%	ELIANA (25th Apr 2017)[50]
Average length of hospitalisation stay (days)	25.85	ELIANA (25th Apr 2017)[50]
Average cost per day of hospitalisation	£772.11	Based on NHS Reference Costs 2016–2017 (Weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with

		length of stay 1 day or more PM40A–PM40C)[114]
Total cost of hospitalisation	***£19,959.03***	Calculation
Cost of ICU (not due to CRS)	**Input**	**Source / Assumptions**
Average length of ICU stay (days)	1.78	ELIANA (25th Apr 2017)[50]
Average daily cost of ICU stay	£1,559.68	Based on NHS Reference Costs 2016-2017 (Weighted average of: Paediatric Critical Care [excluding transportation] XB01Z–XB07Z, XB09Z)[114]
Total cost of ICU stay	***£2776.22***	Calculation
Total tisagenlecleucel infusion costs	**£304,735.26**	**Calculation**

Abbreviations: ICU: intensive care unit; NHS: National Health Service.

Salvage chemotherapy (FLA-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 FLA-IDA (fludarabine, cytarabine and idarubicin).[2] As such, the costs of salvage chemotherapy within the model were based on the drug acquisition and administration costs associated with treatment with the FLA-IDA regimen.

The dosing regimen of FLA-IDA was based on a protocol from the NHS Network Site Specific Group and validated with UK clinical experts and comprised 1 cycle of:[2, 91]

- Fludarabine 30 mg/m^2 daily for 5 doses;
- Cytarabine 2 mg/m^2 daily for 5 doses;
- Idarubicin 8 mg/m^2 daily for 3 doses.

Feedback from UK clinical experts was that the FLA-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.[2] As such, and in the absence of any clinical trial data to suggest otherwise, it was conservatively assumed in the model that all administration costs would be covered by the daily cost of hospitalisation and that patients would remain in hospital for 21 days. A summary of the costs associated with salvage chemotherapy (FLA-IDA) is presented in Table 48.

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):[35]

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

    - Days 8–28: 15 mcg/m^2/day
- Cycle 2 and subsequent cycles (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–28: 15 mcg/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 epidemiological data (8.3%).

The dose of blinatumomab for patients over the age of 18 was based on the blinatumomab SmPC.[92]

- Cycle 1 (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–7: 9 mcg /day
    - Days 8–28: 28 mcg /day
- Cycle 2 and subsequent cycles (4 weeks followed by a 2-week treatment-free interval):
    - Days 1–28: 28 mcg /day

The average dose required per infusion was based on an average BSA of [redacted] for patients <18 years (based on the ELIANA [31st Dec 2017] and ENSIGN [6th Oct 2017) trials; height IPD were not available for the B2101J study).[47, 48] 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, but was instead explored as a scenario analysis.[2]

Hospitalisation costs were applied in accordance with the hospitalisation 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.[92] 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 £772.11, based on NHS Reference Costs 2016–2017 (Weighted average of Elective Inpatient Excess Bed Days, Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more PM40A–PM40C).[114] Patients receiving blinatumomab in the outpatient setting were assumed to include a daily outpatient administration cost of £205.09, based on NHS Reference Costs 2016–2017 (Chemotherapy, Outpatient, SB15Z, Deliver Subsequent Elements of a Chemotherapy Cycle) as well as a daily pump set-up cost of £3.89 (inflated from 2014–2015 to 2016–2017 from the cost used in TA450, based on input from UK oncology nurses considering the pump to be a BodyGuard 323™ Ambulatory Infusion Pump).[44, 114]

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.[35] The total costs of blinatumomab included in the economic analysis are summarised in Table 49, 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 5; therefore, treatment with blinatumomab is not anticipated to extend beyond one year and hence discounting is not affected.

Table 48: Salvage chemotherapy (FLA-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	£23.01 (50 mg)	30 mg/m^2 daily	37.8 mg	1	5	£115.05	• The cost per vial of fludarabine and cytarabine are derived from the Drugs and pharmaceutical eMIT[35] • The cost per vial of idarubicin is derived from the BNF Online[11] • The dosing schedules are based on a protocol from the NSSG and validated with UK clinical experts[25, 118] • The average dose required per infusion is based on an average BSA of [redacted] (based on the ELIANA [31st Dec 2017] and ENSIGN [6th Oct 2017) clinical trials; height IPD were not available for the B2101J study)[119, 120]
Cytarabine	£6.13 (1000 mg)	2 mg/m^2 daily	2520.0 mg	3	5	£91.95	
Idarubicin	£87.36 (5 mg)	8 mg/m^2 daily	10.08 mg	3	3	£786.24	
Total cost						**£993.24**	

Abbreviations: BNF: British National; BSA: body surface area; eMIT: electronic market information tool; FLA-IDA: fludarabine, cytarabine and idarubicin.

Table 49: Blinatumomab drug costs for the paediatric dose

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 mcg/m^2/day	5.95	1.00	7	96%	£54,055.60	• The cost per vial of blinatumomab is derived from the BNF Online[9] • 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)[121] • The average dose required per infusion was based on an average BSA of [redacted] for patients <18 years (based on the ELIANA [31st Dec 2017]
Cycle 1 (days 8–28)	£2,017.00 (38.5 mcg)	15 mcg/m^2/day	17.86	1.00	21			
Cycle 2 (days 1–28)	£2,017.00 (38.5 mcg)	15 mcg/m^2/day	17.86	1.00	28	31%	£17,749.60	
Cycle 3 (days 1–28)	£2,017.00 (38.5 mcg)	15 mcg/m^2/day	17.86	1.00	28	10%	£5,647.60	
Cycle 4 (days 1–28)	£2,017.00 (38.5 mcg)	15 mcg/m^2/day	17.86	1.00	28	4%	£2,420.40	

Cycle 5 (days 1–28)	£2,017.00 (38.5 mcg)	15 mcg/m^2/day	17.86	1.00	28	4%	£2,420.40	and ENSIGN [6th Oct 2017) clinical trials; height IPD were not available for the B2101J study)[119, 120]
Total cost							**£82,293.60**	

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.
Abbreviations: BNF: British National Formulary; BSA: body surface area; IPD: individual patient data.

Table 50: Blinatumomab drug costs for the adult dose

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)	9 mcg /day	9.00	1.00	7	96%	£54,055.60	• The cost per vial of blinatumomab is derived from the BNF Online[9] • The dosing schedule is taken from the SmPC for blinatumomab[122] • 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)[121]
Cycle 1 (days 8–28)	£2,017.00 (38.5 mcg)	28 mcg /day	28.00	1.00	21			
Cycle 2 (days 1–28)	£2,017.00 (38.5 mcg)	28 mcg /day	28.00	1.00	28	31%	£17,749.60	
Cycle 3 (days 1–28)	£2,017.00 (38.5 mcg)	28 mcg /day	28.00	1.00	28	10%	£5,647.60	
Cycle 4 (days 1–28)	£2,017.00 (38.5 mcg)	28 mcg /day	28.00	1.00	28	4%	£2,420.40	
Cycle 5 (days 1–28)	£2,017.00 (38.5 mcg)	28 mcg /day	28.00	1.00	28	4%	£2,420.40	
Total cost							**£82,293.60**	

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.
Abbreviations: BNF: British National Formulary; BSA: body surface area; IPD: individual patient data.

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, patiens 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 27. 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 51). The stem cell harvesting and allo-SCT procedure costs were based on NHS Reference Costs 2016–2017.[114] 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.[123] 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 2016–2017 costs using the hospital and community health services (HCHS) index.[124]

Table 51: Subsequent allo-SCT costs

Component	Cost	Source
Stem cell harvesting cost	£3,291.49	NHS Reference Costs 2016–2017: Weighted average of Elective Inpatient SA18Z Bone marrow harvest and SA34Z Peripheral Blood Stem Cell Harvest[114]
Allo-SCT procedure	£71,694.40	NHS Reference Costs 2016–2017: Weighted average of Elective Inpatient Paediatric Bone Marrow Transplant and Peripheral Blood Stem Cell Transplant (SA20B–SA23B, SA38B, SA39B)[114]
Allo-SCT follow-up cost (up to 24 months post allo-SCT)	£41,325.56	UK Stem Cell Strategy Oversight Committee (see detailed calculation in Table 52)[123]
Total cost	**£116,311.44**	

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

Table 52: 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 (202/2013 cost year)			£39,275.00
Total cost (2016/2017 cost year)			**£41,325.56**

Abbreviations: allo-SCT: allogeneic haematopoietic stem cell transplantation; NHS, national health service; UK, United Kingdom.
Source: UK Stem Cell Strategy Oversight Committee.[123]

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 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.[2] 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 53 and Table 54. Table 55 summarises the follow-up costs for all therapies by health state and follow-up year.

For patients receiving salvage chemotherapy (FLA-IDA) and blinatumomab who remained in the EFS state, the frequency of monitoring and follow-up was obtained from the UK Leukaemia and Lymphoma research guideline.[125] As the specific laboratory tests and procedures were not specified in the UK Leukaemia and Lymphoma research guideline, these items were obtained from the National Comprehensive Cancer Network (NCCN) guideline.[39] For patients receiving tisagenlecleucel who remain in the EFS state, the frequency of monitoring and follow-up was derived from the ELIANA trial protocol.[63] 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 (FLA-IDA) during Year 1. 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. All unit costs were derived from NHS reference costs 2016–2017.[114]

Table 53: 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	£228.25	12	4	2	1	NHS Reference Costs 2016–2017: Consultant Led, WF01A–260, Paediatric Medical Oncology[114]
Haematology panel	£3.06	16	4	2	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS05, Haematology[114]
Coagulation panel	£1.69	3	0	0	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[114]
Chemistry panel (including liver function test)	£1.13	16	4	2	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[114]
CSF	£205.66	1	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, HC72B–420, Paediatrics[114]
Serum test	£1.69	5	0	0	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[114]
B-cell and T-cell test	£3.06	8	2	2	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS05, Haematology[114]
ECG	£499.24	1	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, EY51Z-303, Clinical Haematology[114]
Bone marrow aspirate	£288.46	3	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, SA33Z–303, Clinical Haematology[114]
Bone marrow biopsy	£288.46	3	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, SA33Z–303, Clinical Haematology[114]
Echocardiogram	£242.41	0	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, EY50Z–303, Clinical Haematology[114]
Liver function test	£1.13	0	0	0	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[114]
Salvage chemotherapy (FLA-IDA) and blinatumomab						

Consultant visit	£228.25	6	4	2	1	NHS Reference Costs 2016–2017: Consultant Led, WF01A–260, Paediatric Medical Oncology[114]
Haematology panel	£3.06	6	4	2	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS05, Haematology[114]
CSF	£205.66	1	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, HC72B–420, Paediatrics[114]
Bone marrow aspirate	£288.46	1	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, SA33Z–303, Clinical Haematology[114]
Echocardiogram	£242.41	1	0	0	0	NHS Reference Costs 2016–2017: Outpatient Procedures, EY50Z–303, Clinical Haematology[114]
Liver function test	£1.13	6	0	0	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[114]

[a]Follow up frequencies for tisagenlecleucel were derived from ELIANA.[63] Follow up frequencies for chemotherapy regimens based on UK-specific Leukaemia and Lymphoma research guideline[125] and the service items were based on NCCN guideline.[39]
Abbreviations: CSF: cerebrospinal fluid; ECG: electrocardiogram; NHS: National Health Service.

Table 54: Follow-up schedule and unit cost inputs for patients in the PD health state

Parameter	Unit cost	Yearly frequency[a]	Source
Consultant visit	£228.25	6	NHS Reference Costs 2016–2017: Consultant Led, WF01A–260, Paediatric Medical Oncology[114]
Haematology panel	£3.06	6	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS05, Haematology[114]
Coagulation panel	£1.69	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[114]
Chemistry panel (including liver function test)	£1.13	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[114]
CSF	£205.66	1	NHS Reference Costs 2016–2017: Outpatient Procedures, HC72B–420, Paediatrics[114]
Serum test	£1.69	0	NHS Reference Costs 2016-2017: Directly Accessed Patient Services, DAPS03, Integrated Blood Services[114]
B cell and T cell test	£3.06	0	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS05, Haematology[114]
ECG	£499.24	0	NHS Reference Costs 2016–2017: Outpatient Procedures, EY51Z–303, Clinical Haematology[114]
Bone marrow aspirate	£288.46	1	NHS Reference Costs 2016–2017: Outpatient Procedures, SA33Z–303, Clinical Haematology[114]
Bone marrow biopsy	£288.46	0	NHS Reference Costs 2016–2017: Outpatient Procedures, SA33Z–303, Clinical Haematology[114]
Echocardiogram	£242.41	1	NHS Reference Costs 2016–2017: Outpatient Procedures, EY50Z–303, Clinical Haematology[114]
Liver function test	£1.13	6	NHS Reference Costs 2016–2017: Directly Accessed Patient Services, DAPS04, Clinical Biochemistry[114]

[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.[125]
Abbreviations: CSF: cerebrospinal fluid; ECG: electrocardiogram; NHS: National Health Service; UK: United Kingdom.

Table 55: Follow-up cost inputs summary (monthly cost by treatment)

Health state and year	Tisagenlecleucel	Salvage chemotherapy	Blinatumomab
EFS (year 1)	£439.97	£177.59	£177.59
EFS (year 2)	£77.99	£77.10	£77.10
EFS (year 3–5)	£39.25	£38.55	£38.55
EFS (post 5 years)	£38.04	£19.02	£19.02
PD	£177.59	£177.59	£177.59
Long-term survivors (EFS and PD)	£19.02	£19.02	£19.02

Abbreviations: EFS: event-free survival; PD: progressive disease.
Source: ELIANA trial protocol;[63] Leukaemia and Lymphoma research guideline;[125] NCCN guidelines;[39] NHS Reference Costs 2016–2017.[114]

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. The cost of terminal care was assumed to be £7,508.76, based on a weighted average of NHS Reference Costs 2016–2017 Non-Elective Inpatient Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more (PM40A–PM40C).[114]

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 pooled analysis of patients who received tisagenlecleucel infusion (i.e. the full analysis set; n=[redacted]) in all three tisagenlecleucel clinical trials: ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017) and B2101J (30th Jan 2017 data cut-off).[88, 119, 120] For blinatumomab, AE rates were derived from von Stackelberg *et al.* (2016) and for salvage chemotherapy (FLA-IDA), in the absence of any clinical evidence, the AE rates from Jeha *et al.* (2006) were used.[121, 126] The costs associated with the treatment of each AE were derived from NHS Reference Costs 2016–2017.

The rates and unit costs of the AEs included within the economic model are presented in Table 58.

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 (31st Dec 2017) and von Stackelberg *et al.* (2016) clinical trials.[35, 47]

The average length of ICU stay was estimated to be [redacted] days, based on the average length of ICU stay for all patients who experienced CRS (of any grade) in the ELIANA trial (31st Dec 2017).[47] Feedback from UK clinical experts was that [redacted] days can be considered an overestimate and that, in clinical practice, patients might only remain in ICU for 48 hours.[2] Furthermore, the ICU length of stay for CRS 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. The average daily cost per ICU stay was based on NHS Reference Costs 2016–2017 and a weighted average of Paediatric Critical Care (XB01Z-XB07Z, XB09Z).[114] The detailed resource use inputs considered in the CRS AE cost estimation are listed in Table 56.

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 56: 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			**£18,029.19**
Paediatric ICU admission	£1,559.68	[redacted][a]	
Tocilizumab treatment	£579.54	[redacted]	

[a]Note the average length of ICU stay for CRS was estimated to be [redacted] days, based on the average length of ICU stay for all patients who experienced CRS (of any grade, not just grade 3 or 4) in the ELIANA trial (31st Dec 2017).
Abbreviations: CRS: cytokine release syndrome; ICU: intensive care unit.
Source: BNF 2018 (tocilizumab);[127] ELIANA CSR (31st Dec 2017).[47]

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% patients with tisagenlecleucel infusion would receive IVIG based on data from the ELIANA trial (25th Apr 2017), and the median time to B-cell recovery was assumed the median treatment duration (11.4 months).[50, 128] 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 2018.[84, 129]

A monthly outpatient administration cost was included and was based on NHS Reference Costs 2016–2017 Chemotherapy, SB12Z, Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance.[114] The total IVIG cost was calculated to be £11,284.84 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 57 presents the detailed dosing and unit costs for B-cell aplasia.

Table 57: 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	Total IVIG cost
IVIG drug cost						
IVIG	£1,020.00 20,000 mg	500 mg/kg every 4 weeks	£1,349.86	£269.86	11.40 months	**£11,284.82**
IVIG	£30.00 500 mg					

[a]The model considered one infusion per cycle in the calculation of total administration cost per cycle.
Abbreviations: IVIG: intravenous immunoglobulin.
Source: BNF 2018 (IVIG);[130] ELIANA CSR (25th Apr 2017).[50]

Table 58: 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	Pooled analysis[a] (ELIANA, ENSIGN and B2101J)[47-49]	Jeha *et al.* (2006)[34,b]	von Stackelberg *et al.* (2016)[35,c]		
Acute kidney injury	[redacted]	-	-	£659.42	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Renal Disease with Renal Failure (PL38A–PL38C)[114]
Alanine aminotransferase increased	[redacted]	-	15.71%	£469.04	NHS Reference Costs 2016–2017: Day Case Liver Failure Disorders without Interventions (GC01F)[114]
Anaemia	[redacted]	-	35.71%	£315.50	NHS Reference Costs 2016–2017: 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)[114]
Anorexia	-	19.67%	-	£315.65	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Eating Disorders (PT53A–PT53B)[114]
Aspartate aminotransferase increased	[redacted]	-	11.43%	£469.04	NHS Reference Costs 2016–2017: Day Case Liver Failure Disorders without Interventions (GC01F)[114]
Bacteraemia	-	13.11%	-	£389.68	Cost of bacteraemia is assumed to equal the cost of sepsis[114]
Blood bilirubin increased	[redacted]	-	-	£805.78	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric, Hepatobiliary or Pancreatic Disorders (PG71A–PG71C)[114]
Capillary leak syndrome	[redacted]	-	-	£615.11	NHS Reference Costs 2016–2017: Fluid or Electrolyte Disorders, with Interventions (KC05G)[114]

Cytokine-release syndrome	[redacted]	-	5.71%	£18,029.19	(See Table 56)
Decreased appetite	[redacted]	-	-	£315.65	Cost of decreased appetite is assumed to equal the cost of anorexia[114]
Dermatitis	-	11.48%	-	£359.25	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric, Rash or Other Non-Specific Skin Eruption (PJ66A–PJ66C)[114]
Diarrhoea	-	13.11%	-	£556.93	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Other Gastrointestinal Disorders (PF26A– PF26C)[114]
Encephalopathy	[redacted]	-	-	£641.75	NHS Reference Costs 2016–2017: Weighted average of Day Case Cerebrovascular Accident, Nervous System Infections or Encephalopathy (AA22C–AA22G)[114]
Epistaxis	-	13.11%	-	£1,528.01	NHS Reference Costs 2016–2017: Day Case Major Treatment of Epistaxis (CA12Z)[114]
Febrile neutropenia	[redacted]	49.18%	17.14%	£435.66	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Febrile Neutropenia with Malignancy (PM45A–PM45D)[114]
Hallucination	-	13.11%	-	£359.12	NHS Reference Costs 2016–2017: Day Case Schizophrenia, Schizotypal or Delusional Disorders, treated by a Non-Specialist Mental Health Service Provider (WD07Z)[114]
Haemoglobin	[redacted]	-	-	£307.23	NHS Reference Costs 2016–2017: Weighted average of Day Case Iron Deficiency Anaemia (SA04G–SA04L)[114]
Hepatomegaly	-	11.48%	-	£463.84	NHS Reference Costs 2016–2017: Weighted average of Day Case Liver Failure Disorders without Interventions (GC01E–GC01F)[114]
Hypertension	-	9.84%	5.71%	£413.09	NHS Reference Costs 2016–2017: Day Case Hypertension (EB04Z)[114]
Hypocalcaemia	[redacted]	-	-	£331.92	NHS Reference Costs 2016–2017: Weighted average of Day Case Fluid or Electrolyte Disorders (KC05G–KC05H), with Interventions and Fluid or

					Electrolyte Disorders, without Interventions (KC05J–KC05N)[114]
Hypokalaemia	[redacted]	-	17.14%	£331.92	Cost of hypokalaemia is assumed to equal the cost of hypocalcaemia
Hypophosphataemia	[redacted]	-	-	£331.92	Cost of hypophosphatemia is assumed to equal the cost of hypocalcaemia
Hypotension	[redacted]	18.03%	-	£413.09	Cost of hypotension is assumed to equal the cost of hypertension
Hypoxia	[redacted]	-	-	£384.07	Cost of hypoxia is assumed to equal the cost of respiratory distress/failure
Leukopenia	[redacted]	-	10.00%	£329.68	NHS Reference Costs 2016–2017: Weighted average of Day Case Agranulocytosis (SA35A–SA35E)[114]
Lymphocyte count decreased	[redacted]	-	-	£329.68	Cost of lymphocyte count decreased is assumed to equal the cost of leukopenia
Nausea	[redacted]	16.39%	-	£523.89	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric, Feeding Difficulties or Vomiting (PF28A–PF28E)[114]
Neutropenia	[redacted]	14.75%	17.14%	£329.68	Cost of neutropenia is assumed to equal the cost of leukopenia
Neutrophil count decreased	[redacted]	-	12.86%	£329.68	Cost of neutrophil count decreased is assumed to equal the cost of leukopenia
Petechiae	-	11.48%	-	£460.26	Cost of petechiae is assumed to equal the cost of coagulopathy
Platelet count decreased	[redacted]	-	14.29%	£325.11	NHS Reference Costs 2016–2017: Weighted average of Day Case Thrombocytopenia (SA12G–SA12K)[114]
Pleural effusion	-	9.84%	-	£415.10	Cost of pleural effusion is assumed to equal the cost of pulmonary oedema
Pneumonia	-	9.84%	-	£612.58	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis (PD14A–PD14F)[114]

Pulmonary oedema	[redacted]	-	-	£415.10	NHS Reference Costs 2016–2017: Weighted average of Day Case Pulmonary Oedema with Interventions (DZ20D) and Pulmonary Oedema without Interventions (DZ20E–DZ20F)[114]
Pyrexia	[redacted]	14.75%	14.29%	£380.75	NHS Reference Costs 2016–2017: Weighted average of Day Case Paediatric Fever of Unknown Origin (PW20A–PW20C)[114]
Respiratory distress	-	11.48%	-	£384.07	NHS Reference Costs 2016–2017: Weighted average of Day Case Respiratory Failure with Single Intervention (DZ27Q– DZ27R) and Respiratory Failure without Interventions (DZ27S–DZ27U)[114]
Sepsis	-	13.11%	-	£389.68	NHS Reference Costs 2016–2017: Weighted average of Sepsis without Interventions (WJ06G–WJ06J)[114]
Staphylococcal bacteraemia	-	9.84%	-	£389.68	Cost of staphylococcal bacteraemia is assumed to equal the cost of sepsis
Thrombocytopenia	[redacted]	-	21.43%	£325.11	NHS Reference Costs 2016–2017: Weighted average of Day Case Thrombocytopenia (SA12G–SA12K)[114]
White blood cell count decreased	[redacted]	-	10.00%	£329.68	Cost of WBC count decreased is assumed to equal the cost of leukopenia
Total AE Costs	**£9,409.69**	**£1,335.68**	**£1,760.76**		

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]Pooled analysis of ELIANA (31st Dec 2017), ENSIGN (6th Oct 2017), B2101J (30th Jan 2017 data cut-off). Based on grade 3 or 4 AEs, regardless of study drug relationship, occurring any time post tisagenlecleucel infusion in >5% patients.
[b]Jeha *et al.* (2016). Based on grade ≥3 AEs, regardless of causality that occurred in ≥10% of patients in all cycles.[34]
[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.
Source: ELIANA CSR (31st Dec 2017);[47]; ENSIGN CSR (6th Oct 2017);[48] B2101J CSR (30th Jan 2017);[49] von Stackelberg *et al.* (2016)[35]; Jeha *et al.* (2006).[34]

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 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the key base case analysis inputs is presented in Table 59.

Table 59: 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
Discount rate (benefits)	3.50%	
Time horizon	88 years	
Patient characteristics		
Starting age (years)	[redacted]	Section B.3.3.1
Percent female	[redacted]	
Mean BSA	[redacted]	
Mean weight (kg)	[redacted]	
Efficacy		
OS distribution (tisagenlecleucel)	Mixture cure exponential	Section B.3.3.3
EFS distribution (tisagenlecleucel)	Mixture cure generalised gamma	
OS distribution (salvage chemotherapy [FLA-IDA])	Generalised gamma	
EFS distribution (salvage chemotherapy [FLA-IDA])	Based on OS	
OS distribution (blinatumomab)	Mixture cure lognormal	
EFS distribution (blinatumomab)	Based on OS	
Subsequent allo-SCT		
Subsequent allo-SCT rate for tisagenlecleucel	[redacted]	Section B.3.5.1
Subsequent allo-SCT rate for salvage chemotherapy (FLA-IDA)	16.39%	
Subsequent allo-SCT rate for blinatumomab	34.29%	
Allo-SCT disutility (per month)	-0.048	Section B.3.4.5
Allo-SCT cost	£116,311.44	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	-0.03	Section B.3.4.4
Disutility for salvage chemotherapy	-0.02	

Disutility for blinatumomab	-0.01	
Health state costs		
Follow-up medical costs per cycle in EFS for tisagenlecleucel	Year 1: £439.97 Year 2: £77.99 Year 3-5: £39.25 Year 5+: £19.02	Section B.1.1.1
Follow-up medical costs per cycle in EFS for comparators	Year 1: £177.59 Year 2: £77.10 Year 3-5: £38.55 Year 5+: £19.02	
Medical costs per cycle in PD	£177.59	
One-time terminal care cost	£7,508.76	
Drug acquisition and administration		
Pre-treatment costs	Tisagenlecleucel: £9,584.12	Section B.3.5.1
Treatment costs		
Procedure/treatment	Tisagenlecleucel: £282,000.00 Salvage chemotherapy: £993.24 Blinatumomab: £82,293.60	Section B.3.5.1
Outpatient administration cost	Blinatumomab: £6,594.91	
Hospitalisation cost	Tisagenlecleucel: £22,735.26 Salvage chemotherapy: £16,214.30 Blinatumomab: £7,136.50	
Cost of AEs		
AEs	Tisagenlecleucel: £19,893.07 Salvage chemotherapy: £1,335.68 Blinatumomab: £1,760.76	Section B.3.5.3

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.3.6.2 Assumptions

A list of the assumptions used in the base case analysis is provided in Table 60 malongside 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.3.8.3.

Table 60: List of assumptions for the base case analysis

Parameter	Assumption	Justification/Exploration 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

Subsequent allo-SCT	The efficacy benefits of receipt of subsequent allo-SCT were captured in the EFS and OS estimations for all treatments as a result of using the direct trial data • It was assumed that the proportions of patients receiving subsequent allo-SCT in the clinical trial data sources were reflective of UK clinical practice	• Expert UK clinician feedback supported this assumption
Patients who remain alive at 5 years in the model can be considered to be effectively cured	• Patients still alive in the model at 5 years were considered to be effectively cured • These patients were associated with a risk of death equal to general population mortality, adjusted by a SMR* • After 5 years, EFS was assumed to flatten up until it hit OS (i.e. no further relapse events), reflecting that patients were effectively cured and therefore not at risk of relapse and only associated with a risk of death as described above *Note this assumption did not apply to the mixture cure models, which implicitly already assume a proportion of cured patients.	• It has been established previously that patients with ALL who remain alive in the mid-term can be considered effectively cured. • This assumption was utilised in NICE TA450 (note: whilst a timepoint of 5 years was preferred by the ERG, the manufacturer assumed a timepoint of 4 years and the NICE Committee considered a timepoint of 4 years to be conservative). • In the NICE mock appraisal of regenerative therapies, this assumption was similarly employed. • Expert clinician feedback consulted as part of this submission confirmed this assumption. • The specific timepoint from which an cure was assumed (5 years in the base case) was explored in scenario analyses
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.[104]	• In the absence of EFS data, this approach was consistent with the approach taken in the NICE mock appraisal.[84] • EFS has been demonstrated to be highly correlated with OS.[106] • Scenario analyses explored the use of RFS data from the von Stackelberg *et al.* (2016) study
Patients in the tisagenlecleucel arm who do not receive tisagenlecleucel infusion are assumed to receive comparator therapies	• 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 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	• This was considered a realistic representation of what would happen in clinical practice, confirmed by expert UK clinician feedback

	QALYs for the comparator arms. A 50/50 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

Abbreviations: allo-SCT, haematopoietic stem cell transplantation; EFS, event-free survival; OS, overall survival; ALL, acute lymphoblastic leukaemia; AE, adverse event; CRS; cytokine-release syndrome

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

A summary of the deterministic base case economic analysis results is presented in Table 61 (with tisagenlecleucel at list price) and Table 62 (with tisagenlecleucel at PAS price).

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

When tisagenlecleucel is provided to the NHS with the confidential PAS discount ([redacted]), tisagenlecleucel is associated with incremental costs of [redacted] and [redacted] versus salvage chemotherapy and blinatumomab, respectively, and the resulting ICERs versus salvage chemotherapy and blinatumomab are £25,404 and £18,392 per QALY gained.

Considered under the end-of-life criteria that are relevant to tisagenlecleucel in this appraisal (see Section B.2.14), these base case ICERs (both with and without the PAS) fall below £30,000 per QALY and well below the cost-effectiveness threshold adopted by NICE for end-of-life conditions of £50,000 per QALY gained.

Table 61: Deterministic base case results (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 62: Deterministic base-case results (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392

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

A summary of the disaggregated costs and QALYs per health state is presented in Appendix J.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted using a Monte-Carlo simulation with 2,000 iterations. In each iteration, the model inputs were randomly drawn from the specified distributions summarised in Table 63. 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]).[131]

A complete list of the PSA inputs is presented in in Table 63 and the results of the PSA (2,000 iterations) are presented in Table 64 (with tisagenlecleucel at list price) and Table 65 (with tisagenlecleucel at PAS price). 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.

Scatter plots showing the incremental costs and QALYs for tisagenlecleucel (list price) versus salvage chemotherapy (FLA-IDA) and blinatumomab are presented in Figure 40 and Figure 41, respectively (with tisagenlecleucel at list price); and in Figure 42 and Figure 43, respectively (with tisagenlecleucel at PAS price.

Table 63: PSA inputs

Parameter	Distribution	Mean	SE	Alpha	Beta
Efficacy					
Parametric estimate for OS/EFS	Bootstrapping	-	-	-	-
EFS versus OS ratio - salvage chemotherapy	Lognormal	0.83	0.21	-	-
EFS versus OS ratio - blinatumomab	Lognormal	0.83	0.21	-	-
Decision tree					
Proportion of patients assigned to tisagenlecleucel who continue to infusion	Dirichlet	[redacted]	[redacted]	-	-
Proportion of patients assigned to tisagenlecleucel who discontinue prior to infusion due to AEs or manufacturing failure	Dirichlet	[redacted]	[redacted]	-	-
Proportion of patients assigned to tisagenlecleucel who die prior to infusion	Dirichlet	[redacted]	[redacted]	-	-
Proportion of patients continuing to infusion who receive leukapheresis and cryopreservation costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients continuing to infusion who receive bridging chemotherapy costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients continuing to infusion who receive lymphodepleting chemotherapy costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients discontinuing prior to infusion due to AEs or manufacturing failure who receive leukapheresis and cryopreservation costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients discontinuing prior to infusion due to AEs or manufacturing failure who receive bridging chemotherapy costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients discontinuing prior to infusion due to AEs or manufacturing failure who receive lymphodepleting chemotherapy costs	Beta	[redacted]	[redacted]	0.00	0.00
Proportion of patients who discontinue prior to infusion, and receive salvage chemotherapy	Beta	[redacted]	[redacted]	7.50	7.50
Proportion of patients who discontinue prior to infusion, and receive blinatumomab	n/a	[redacted]	[redacted]	-	-
Proportion of patients who die prior to infusion who receive leukapheresis and cryopreservation costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients who die prior to infusion who receive bridging chemotherapy costs	Beta	[redacted]	[redacted]	-1.00	0.00
Proportion of patients who die prior to infusion who receive lymphodepleting chemotherapy costs	Beta	[redacted]	[redacted]	0.00	0.00
Pre-treatment costs (tisagenlecleucel)					

Cost for leukapheresis	Gamma	1020.08	255.02	16.00	63.75
Drug cost for bridging chemotherapy	Gamma	178.66	44.67	16.00	11.17
Drug cost for lymphodepleting chemotherapy	Gamma	122.46	30.62	16.00	7.65
Outpatient administration cost for bridging chemotherapy	Gamma	1759.67	439.92	16.00	109.98
Outpatient administration cost for lymphodepleting chemotherapy	Gamma	300.02	75.01	16.00	18.75
Hospitalisation costs for lymphodepleting chemotherapy	Gamma	7101.38	1775.34	16.00	443.84
Treatment costs					
Outpatient administration cost for tisagenlecleucel	Gamma	[redacted]	[redacted]	16.00	0.87
Hospitalisation cost for tisagenlecleucel	Gamma	[redacted]	[redacted]	16.00	1181.78
ICU cost for tisagenlecleucel	Gamma	[redacted]	[redacted]	16.00	173.51
Drug cost for salvage chemotherapy	Gamma	993.24	248.31	16.00	62.08
Outpatient administration cost for salvage chemotherapy	Gamma	0.00	0.00	0.00	0.00
Hospitalisation cost for salvage chemotherapy	Gamma	16214.30	4053.58	16.00	1013.39
Drug cost for blinatumomab	Gamma	57605.52	14401.38	16.00	3600.35
Outpatient administration cost for blinatumomab	Gamma	6594.91	1648.73	16.00	412.18
Hospitalisation cost for blinatumomab	Gamma	7136.50	1784.12	16.00	446.03
Utility					
EFS	Beta	0.91	0.02	-	-
Relapsed/progressed disease	Beta	0.75	0.16	-	-
Disutility					
Tisagenlecleucel	Beta	0.03	0.01	15.49	505.41
Salvage chemotherapy	Beta	0.02	0.01	15.59	629.54
Blinatumomab	Beta	0.01	0.00	15.82	1471.56
ICU disutility for CRS following blinatumomab	Beta	0.00	0.00	15.97	10084.84
ICU disutility for CRS following tisagenlecleucel	Beta	0.01	0.00	15.80	1311.60
ICU disutility for non-CRS following tisagenlecleucel	Beta	0.00	0.00	15.92	3572.46
AE costs					

Tisagenlecleucel	Gamma	[redacted]	[redacted]	16.00	588.11
Salvage chemotherapy	Gamma	1335.68	333.92	16.00	83.48
Blinatumomab	Gamma	1760.76	440.19	16.00	110.05
CRS cost	Gamma	18029.19	4507.30	16.00	1126.82
Follow-up costs					
Follow-up at Year 1 for EFS following tisagenlecleucel	Gamma	439.97	109.99	16.00	27.50
Follow-up at Year 2 for EFS following tisagenlecleucel	Gamma	77.99	19.50	16.00	4.87
Follow-up at Year 3–5 for EFS following tisagenlecleucel	Gamma	39.25	9.81	16.00	2.45
Follow-up post Year 5 for EFS following tisagenlecleucel	Gamma	19.02	4.76	16.00	1.19
Follow-up for PD following tisagenlecleucel	Gamma	177.59	44.40	16.00	11.10
Follow-up at Year 1 for EFS following salvage chemotherapy	Gamma	177.59	44.40	16.00	11.10
Follow-up at Year 2 for EFS following salvage chemotherapy	Gamma	77.10	19.28	16.00	4.82
Follow-up at Year 3–5 for EFS following salvage chemotherapy	Gamma	38.55	9.64	16.00	2.41
Follow-up post Year 5 for EFS following salvage chemotherapy	Gamma	19.02	4.76	16.00	1.19
Follow-up for PD following salvage chemotherapy	Gamma	177.59	44.40	16.00	11.10
Follow-up at Year 1 for EFS following blinatumomab	Gamma	177.59	44.40	16.00	11.10
Follow-up at Year 2 for EFS following blinatumomab	Gamma	77.10	19.28	16.00	4.82
Follow-up at Year 3–5 for EFS following blinatumomab	Gamma	38.55	9.64	16.00	2.41
Follow-up post Year 5 for EFS following blinatumomab	Gamma	19.02	4.76	16.00	1.19
Follow-up for PD following blinatumomab	Gamma	177.59	44.40	16.00	11.10
Terminal care					
Terminal care	Gamma	7508.76	1877.19	16.00	469.30
Subsequent allo-SCT					
Tisagenlecleucel	Beta	[redacted]	[redacted]	31.83	160.17
Salvage chemotherapy	Beta	0.16	0.05	9.84	50.16
Blinatumomab	Beta	0.34	0.06	23.66	45.34
Subsequent allo-SCT cost	Gamma	116311.44	29077.86	16.00	7269.47

Subsequent allo-SCT disutility	Beta	0.57	0.14	6.31	4.76
Patient characteristics					
Age	Normal	[redacted]	[redacted]	-	-
Weight	Normal	[redacted]	[redacted]	-	-
BSA	Normal	[redacted]	[redacted]	-	-
Gender	Beta	[redacted]	[redacted]	74.15	84.85
SMR					
Year 2–5	Lognormal	9.05	0.08	-	-
Year 5–9	Lognormal	9.05	0.08	-	-
Year 10+	Lognormal	9.05	0.08	-	-

Abbreviations: AE: adverse event; ALL: acute lymphoblastic leukaemia; BSA: body surface area; allo-SCT: allogeneic stem cell transplantation; EFS: event-free survival; OS: overall survival; PD: progressive disease; SE: standard error; SMR: standardised mortality ratio.

Table 64: Probabilistic results (tisagenlecleucel list price)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 65: Probabilistic results (tisagenlecleucel PAS price: [redacted] discount)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY
Tisagenlecleucel	[redacted]	[redacted]			
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£27,066
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£20,046

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

Figure 40: Cost-effectiveness plane: tisagenlecleucel (list price) versus salvage chemotherapy (FLA-IDA)

Abbreviations: FLA-IDA: fludarabine, cytarabine and idarubicin; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 41: Cost-effectiveness plane: tisagenlecleucel (list price) versus blinatumomab

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

Figure 42: Cost-effectiveness plane: tisagenlecleucel (PAS price: [redacted] discount) versus salvage chemotherapy (FLA-IDA)

Abbreviations: FLA-IDA: fludarabine, cytarabine and idarubicin; PAS: Patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 43: Cost-effectiveness plane: tisagenlecleucel (PAS price: [redacted] discount) versus blinatumomab

Abbreviations: PAS: Patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

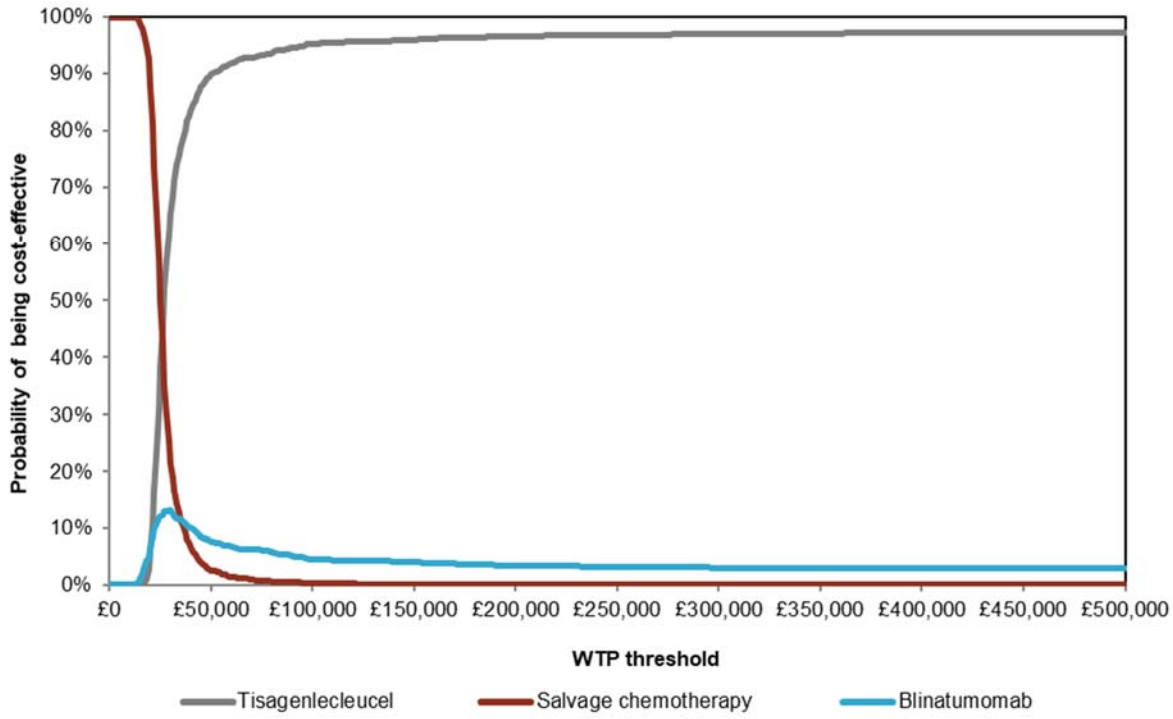
Cost-effectiveness acceptability curves for all comparators with tisagenlecleucel at list price versus are presented in Figure 44 and at PAS price ([redacted] discount) in Figure 45. When considering tisagenlecleucel at list price and a cost-effectiveness threshold of £50,000 per QALY (the threshold considered by NICE for end of life medicines), the probability of tisagenlecleucel being the most cost-effective treatment option is [redacted].

When considering tisagenlecleucel with the confidential PAS discount applied, the probability of tisagenlecleucel being the most cost-effective treatment option is 90% at the £50,000 per QALY gained threshold and 65% at the £30,000 per QALY gained threshold.

Figure 44: Cost-effectiveness acceptability curve for all comparators: tisagenlecleucel (list price)

Abbreviations: FLA-IDA: fludarabine, cytarabine and idarubicin; WTP: willing-ness to pay.

Figure 45: Cost-effectiveness acceptability curve for all comparators: tisagenlecleucel (PAS price: [redacted])



Abbreviations: FLA-IDA: fludarabine, cytarabine and idarubicin; PAS: Patient access scheme; WTP: willingness-to-pay.

B.3.8.2 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 summarised in Table 66 below. Tornado diagrams showing the top twenty drivers of cost-effectiveness in the comparison of tisagenlecleucel versus salvage chemotherapy (FLA-IDA) and blinatumomab are presented in Figure 46 and Figure 47, respectively, when tisagenlecleucel is provided at list price and Figure 48 and Figure 49, respectively, when tisagenlecleucel is provided with the PAS.

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. For blinatumomab, the treatment cost was also key in driving the model outputs. When tisagenlecleucel is provided with the confidential PAS price ([redacted] discount), the DSA does not produce any ICERs that are greater than £27,000 per QALY gained for tisagenlecleucel versus either salvage chemotherapy (FLA-IDA) or blinatumomab.

Table 66: DSA inputs

Parameter	Base case input	DSA inputs		
Efficacy		**Lower value**	**Upper value**	**Variation**
SMR of long-term ALL survivors	9.05	7.77	10.50	95% CI
EFS versus OS ratio for comparators				
Salvage chemotherapy	0.83	0.62	1.00	±25%
Blinatumomab	0.83	0.62	1.00	±25%
Subsequent allo-SCT rate				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	95% CI
Salvage chemotherapy	0.16	0.07	0.26	95% CI
Blinatumomab	0.34	0.23	0.45	95% CI
Utility and disutility (upper utility limit capped at 1)				
Utility for EFS	0.91	0.87	1.00	95% CI
Utility for PD	0.75	0.44	0.91	95% CI
Disutility for tisagenlecleucel				
Treatment	-0.03	-0.02	-0.04	±25%
Short-term AEs	-0.012	-0.009	-0.015	±25%
Long-term AEs	-0.004	-0.003	-0.006	±25%
Disutility for comparators				
Treatment (salvage chemotherapy)	-0.024	-0.018	-0.030	±25%
Treatment (blinatumomab)	-0.011	-0.008	-0.013	±25%
AEs (blinatumomab)	-0.0016	-0.0012	-0.0019	±25%
Subsequent allo-SCT disutility	-0.57	-0.43	-0.71	±25%
Costs				
Pre-treatment costs for tisagenlecleucel				
Leukapheresis	£1,020.88	£765.06	£1,275.09	±25%
Bridging chemotherapy	£85.10	£63.83	£106.38	±25%
Lymphodepleting chemotherapy	£122.46	£91.85	£153.08	±25%
Bridging chemotherapy outpatient administration	£986.07	£739.55	£1,232.59	±25%
Lymphodepleting chemotherapy outpatient administration	£269.04	£201.78	£336.30	±25%
Lymphodepleting chemotherapy hospitalisation	£7,101.38	£5,326.03	£8,876.72	±25%
Treatment cost for tisagenlecleucel				
Outpatient administration cost	£0.00	£0.00	£0.00	±25%
Hospitalisation cost	£19,959.03	£14,969.28	£24,948.79	±25%

ICU cost	£2,776.22	£2,082.17	£3,470.28	±25%
Treatment cost for salvage chemotherapy				
Drug cost	£993.24	£744.93	£1,241.55	±25%
Outpatient administration cost	£0.00	£0.00	£0.00	±25%
Hospitalisation cost	£16,214.30	£12,160.73	£20,267.88	±25%
Treatment cost for blinatumomab				
Drug cost	£82,293.50	£61,720.20	£102,867.00	±25%
Outpatient administration cost	£6,594.91	£4,946.18	£8,243.64	±25%
Hospitalisation cost	£7,136.50	£5,352.37	£8,920.62	±25%
Follow-up cost for tisagenlecleucel				
Year 1	£439.97	£329.97	£549.96	±25%
Year 2–3	£77.99	£58.49	£97.49	±25%
Year 3–4	£39.25	£29.44	£49.06	±25%
Year 5+	£19.02	£14.27	£23.78	±25%
PD	£177.59	£133.20	£221.99	±25%
Follow-up costs for comparators				
Year 1	£177.59	£133.20	£221.99	±25%
Year 2–3	£77.10	£57.83	£96.38	±25%
Year 3–4	£38.55	£28.91	£48.19	±25%
Year 5+	£19.02	£14.27	£23.78	±25%
PD	£177.59	£133.20	£221.99	±25%
Subsequent allo-SCT cost	£116,311.44	£87,233.58	£145,389.30	±25%
AE costs for tisagenlecleucel	£9,409.69	£7,057.27	£11,762.12	±25%
AE costs for salvage chemotherapy	£1,335.68	£1,001.76	£1,669.60	±25%
AE costs for blinatumomab	£1,760.76	£1,320.57	£2,200.95	±25%
CRS cost	£18,029.19	£13,521.89	£22,536.49	±25%
Terminal care cost	£7,508.76	£5,631.57	£9,385.96	±25%
Patient characteristics				
BSA	[redacted]	[redacted]	[redacted]	95% CI
Starting age	[redacted]	[redacted]	[redacted]	95% CI
Proportion female	[redacted]	[redacted]	[redacted]	±25%
Weight	[redacted]	[redacted]	[redacted]	95% CI

Abbreviations: AE: adverse events; BSA: body surface area; CI: confidence interval; CRS: cytokine release syndrome; EFS: event-free survival; EQ-5D: EuroQol-5D; HR: hazard ratio; allo-SCT: haematopoietic stem cell transplantation; IVIG: intravenous immunoglobulin; OS: overall survival; PD: progressive disease; SMR: standardised mortality ratio.

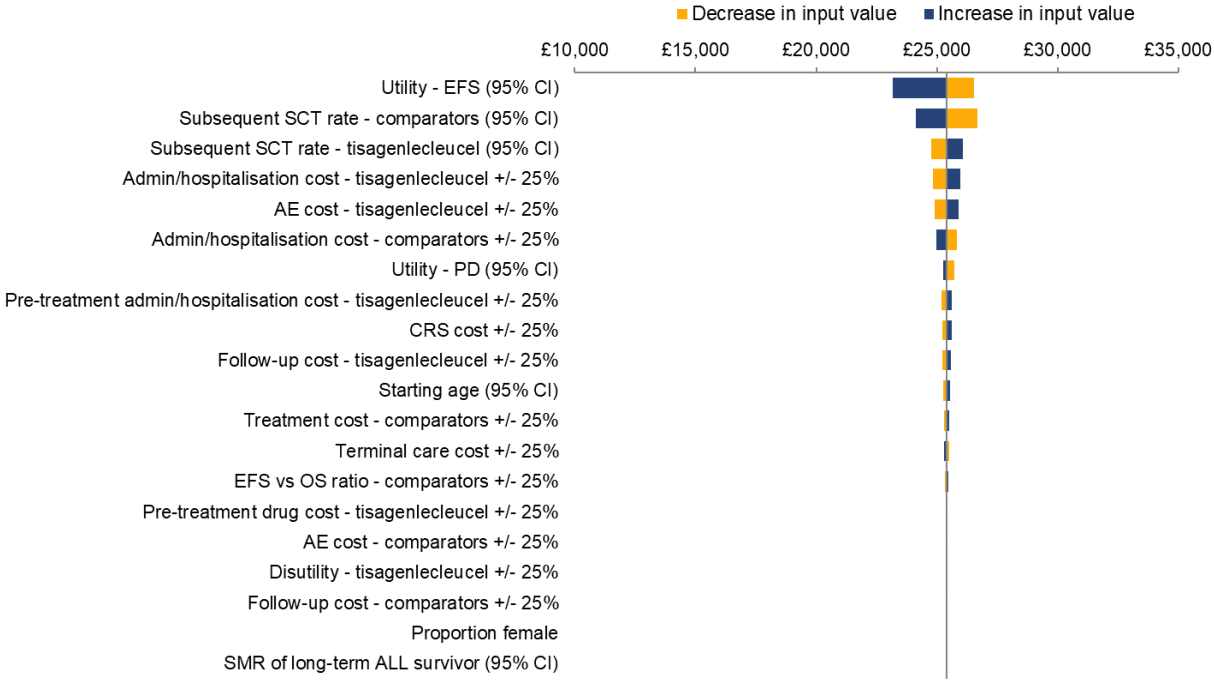
Figure 46: Tornado diagram of the twenty most influential parameters from the DSA: tisagenlecleucel (list price) versus salvage chemotherapy (FLA-IDA)

Abbreviations: DSA: deterministic sensitivity analysis; EFS: event-free survival; FLA-IDA: fludarabine, cytarabine and idarubicin; PD: relapsed/progressed disease; SCT: stem cell transplant.

Figure 47: Tornado diagram of the twenty most influential parameters from the DSA: tisagenlecleucel (list price) versus blinatumomab

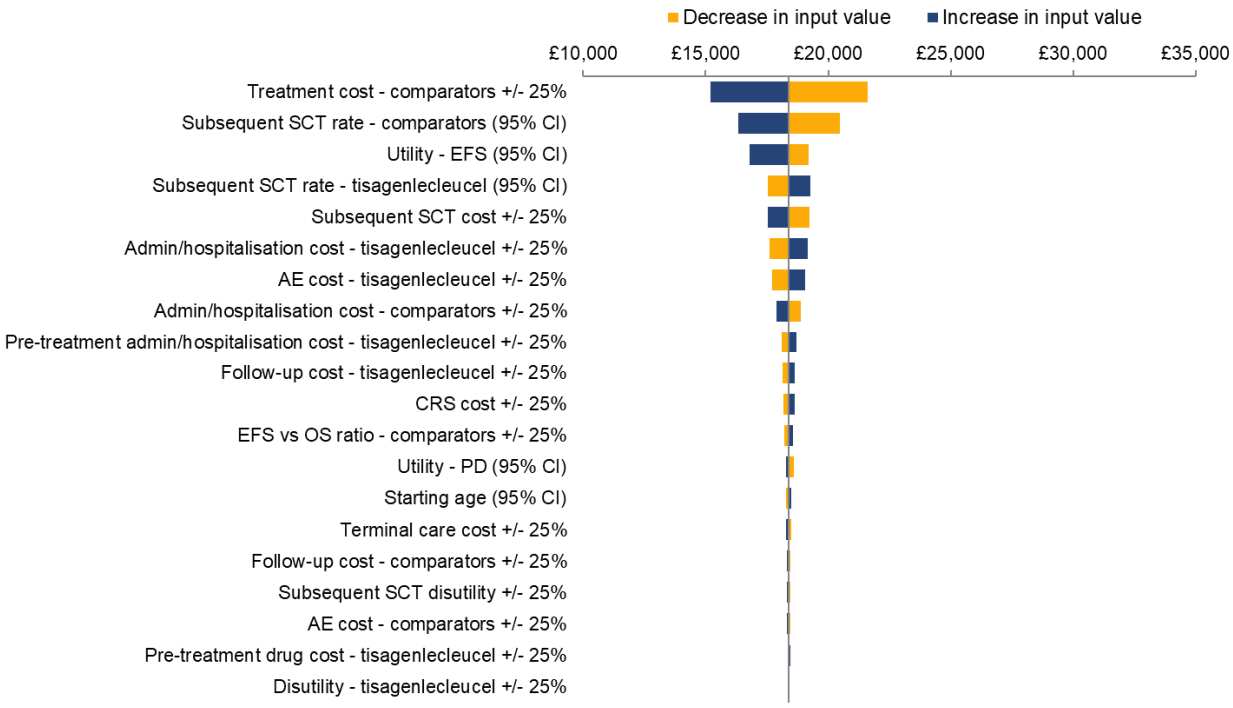
Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; EFS: event-free survival; FLA-IDA: fludarabine, cytarabine and idarubicin; SCT: stem cell transplant.

Figure 48: Tornado diagram of the twenty most influential parameters from the DSA: tisagenlecleucel (PAS price) versus salvage chemotherapy (FLA-IDA)



Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; EFS: event-free survival; FLA-IDA: fludarabine, cytarabine and idarubicin; PAS: patient access scheme; PD: relapsed/progressed disease; SCT: stem cell transplant.

Figure 49: Tornado diagram of the twenty most influential parameters from the DSA: tisagenlecleucel (PAS price) versus blinatumomab



Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; EFS: event-free survival; FLA-IDA: fludarabine, cytarabine and idarubicin; PAS: patient access scheme; PD: relapsed/progressed disease; SCT: stem cell transplant.

B.3.8.3 Scenario analyses

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis and the results of these scenarios are presented from Table 67 to Table 73, with tisagenlecleucel at both list price and PAS price. Across all of the scenarios conducted, it can be demonstrated that changes made to the modelling approach 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. When tisagenlecleucel is provided with the confidential PAS, almost all of the scenarios conducted resulted in ICERs less than £30,000 per QALY gained, which is well below the typically accepted cost-effectiveness threshold of £50,000 for end-of-life medicines.

Cure model approach scenarios

Table 67: Cure model approach scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Alternative OS extrapolation for tisagenlecleucel – log-logistic						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,203
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,284
Scenario: Alternative OS extrapolation for tisagenlecleucel – Gompertz						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,641
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,762
Scenario: Alternative OS extrapolation for blinatumomab – log-logistic						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,368
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,051
Scenario: Blinatumomab EFS based on von Stackelberg RFS – gen. gamma						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,421
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,087

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Standard parametric survival model (plus ALL-adjusted mortality) scenarios

Table 68: Standard parametric survival model (plus ALL-adjusted mortality) scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404

Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Use of standard parametric survival extrapolations for all treatments (OS: tisagenlecleucel gen. gamma, salvage chemotherapy gen. gamma, blinatumomab gen. gamma; EFS: tisagenlecleucel log-logistic, salvage chemotherapy gen. gamma (based on OS), blinatumomab gen. gamma)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,527
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,689
Scenario: Alternative OS extrapolation for tisagenlecleucel – lognormal						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,530
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,574
Scenario: Alternative OS extrapolation for tisagenlecleucel – Gompertz						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,942
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,321
Scenario: Alternative OS extrapolation for tisagenlecleucel – log-logistic						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,799
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,643
Scenario: Alternative OS extrapolation for tisagenlecleucel – weighted by AIC						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,758
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,778
Scenario: Alternative OS extrapolation for blinatumomab – log-logistic						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,637
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,134
Scenario: Alternative OS extrapolation for blinatumomab – lognormal						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,654
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,906
Scenario: Alternative OS extrapolation for blinatumomab – weighted by AIC						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,599
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,634
Scenario: Alternative OS extrapolation for salvage chemotherapy (FLA-IDA) – spline single knot						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,302
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,700
Scenario: Alternative OS extrapolation for salvage chemotherapy (FLA-IDA) – weighted by AIC						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,864
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,722
Scenario: Cure point 2 years						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,842
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,321
Scenario: Cure point 3 years						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,229
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,890

Scenario: Cure point 4 years						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,487
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,771
Scenario: SMR from Armstrong 2016[101]						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,271
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,874
Scenario 15: SMR from Bhatia 2005[103]						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,554
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,030
Scenario 16: SMR from Socié 1999[102]						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,593
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,093

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Alterative efficacy input scenarios

Table 69: Alternative efficacy input scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Tisagenlecleucel efficacy from ELIANA only (OS: Gompertz; EFS: exponential)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,426
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,296
Scenario: Tisagenlecleucel efficacy from ELIANA and ENSIGN only (OS: Gompertz; EFS: exponential)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,407
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,805
Scenario: Salvage chemotherapy efficacy from von Stackelberg 2011 (OS: gen. gamma; EFS: based on OS)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,890
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,737
Scenario: Salvage chemotherapy efficacy from Kantarjian 2017[46] (OS: Spline single knot; EFS: log-logistic)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,743
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,344
Scenario: Salvage chemotherapy efficacy from Hijiya 2011[93] (OS: Weighted using AIC; EFS: based on OS)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,615
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,361

Scenario: Blinatumomab EFS and OS efficacy from RIALTO[75] (Standard parametric survival approach OS: Loglogistic; EFS: Spline single knot)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,732
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,067
Scenario: Blinatumomab OS efficacy from RIALTO[75] (Standard parametric survival approach OS: Loglogistic; EFS: based on OS)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,732
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,059
Scenario: Using the matched tisagenlecleucel population for OS from the MAIC (Standard parametric survival approach OS: Gompertz; EFS log-logistic)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,833
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,203

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Utility values scenarios

Table 70: Utility values scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: ELIANA utility values						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,937
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,907
Scenario: No treatment disutility for blinatumomab						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,403
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,423

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 71: Time horizon and discounting scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: 10-year time horizon						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,663
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,913
Scenario: 20-year time horizon						

Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,397
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,813
Scenario: 40-year time horizon						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,835
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,600
Scenario: 1.5% discount on costs and effects						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,202
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,747
Scenario: 6% discount on costs and effects						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,971
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,683

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Cost scenarios

Table 72: Cost scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Vial sharing						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,110
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,605
Scenario: AE costs set to zero (for all therapies)						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,560
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,930
Scenario: Tocilizumab PAS discount 20%						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,398
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,385

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Decision tree scenarios

Table 73: Decision tree scenarios

	List price			PAS price		
Treatment	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£ per QALY)**
Base case						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404

Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: 100% of patients receive infusion with tisagenlecleucel						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,186
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,575
Scenario: 100% of patients receive infusion with tisagenlecleucel and all pre-treatment costs						
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,247
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,654

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4 Summary of sensitivity analyses results

Results of the sensitivity analyses demonstrate the base case cost-effectiveness results to be robust to the combined distributional uncertainty across model parameters (PSA) and to the majority of changes to the modelling approach that were explored in scenario analyses. The DSA demonstrated that, versus both comparators, the parameters driving the model the most are the EFS utility value and the rate of subsequent SCT, though changes in these parameters did not result in material changes to the base case ICERs. When provided with the confidential PAS discount, tisagenlecleucel was estimated to be 82% cost-effective versus blinatumomab and 91% cost-effective versus salvage chemotherapy (FLA-IDA), under the context of the £50,000 per QALY threshold considered by NICE for end-of-life therapies.

B.3.9 Subgroup analysis

Given the paucity of data for any subgroups, no economic subgroup analyses were conducted as part of this appraisal.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Comprehensive clinician input was sought during the development of the UK cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice to validate the clinical plausibility of the outcomes predicted by the model.

As detailed throughout the submission, the clinical experts were in agreement with the approaches and assumptions taken in the development of the cost-effectiveness model and full details of the clinical validation are provided in the reference pack accompanying this submission. In addition to the validation of survival outcomes, expert clinical opinion was sought to validate the following model inputs:

- Resource use and hospitalisation (length of stay)
- AE rates
- Subsequent allo-SCT rates
- Utility values
- SMR
- Monitoring and follow-up
- Patient baseline characteristics

B.3.11 Interpretation and conclusions of economic evidence

A *de novo* economic analysis was conducted to evaluate 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 for the purposes of this appraisal. 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 salvage chemotherapy (FLA-IDA) and blinatumomab and reflect the most relevant comparators currently 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.

Whilst there were no UK centres in the tisagenlecleucel clinical trials, the patient populations enrolled in the tisagenlecleucel clinical trials can be considered generalisable to the relevant patient population in the UK, based on UK clinical expert feedback. The economic model is underpinned by patient-level data from all three tisagenlecleucel clinical trials. Survival extrapolation was essential to quantify the survival benefit beyond the trial period and a robust and comprehensive approach was followed during the survival extrapolation to ensure the methods were statistically sound, but also clinically plausible. In terms of resource utilisation, all inputs were validated and sourced from UK publications.

A limitation of the cost-effectiveness analysis is that it uses efficacy for clofarabine monotherapy to inform the effectiveness estimates for salvage chemotherapy (FLA-IDA). Whilst there is a lack of published data to support this assumption of equivalence of effectiveness of these therapies in this patient population, clinical feedback was that this assumption was reasonable and that the efficacy between these therapies could be considered comparable in clinical practice. The same efficacy source was also used in the NICE mock appraisal for regenerative therapies.

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 (salvage chemotherapy [FLA-IDA] and blinatumomab). When tisagenlecleucel is provided to the NHS with the confidential PAS discount ([redacted]), the ICERs versus salvage chemotherapy and blinatumomab were £25,404 and £18,392 per QALY gained, respectively. Considered in the context of a disease which affects such a young population, where median OS with current therapies ranges from 3 to 7.5 months, tisagenlecleucel offers patients the potential for a cure. The ICERs with PAS fall below £30,000 per QALY gained and well below the £50,000 per QALY gained threshold considered by NICE for end-of-life medicines. The probability of tisagenlecleucel

being the most cost-effective treatment option was 90% at the £50,000 per QALY gained threshold and 65% at the £30,000 per QALY gained threshold.

As a patient-specific, single infusion therapy, tisagenlecleucel is the first in this class of CAR-T therapy for the treatment of r/r B-cell ALL and represents a paradigm-shift in the treatment approach for this aggressive disease in children and young adults in the UK.

References

1. Novartis Pharmaceuticals Ltd. Tisagenlecleucel. Summary of Product Characteristics (SmPC). [Last accessed: 26 Apr 2018].
2. Novartis Pharmaceuticals UK Ltd. Feedback from UK clinical experts. 2018.
3. 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.
4. National Institute for Health and Care Excellence (NICE). Final Scope: Tisagenlecleucel-T (Kymriah™) for the treatment of patients aged up to 25 years with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse (ID1167) - Issued March 2018.
5. Porter DL, Kalos M, Zheng Z, et al. Chimeric antigen receptor therapy for B-cell malignancies. Journal of Cancer 2011;2:331.
6. 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.
7. Smith AJ, Oertle J, Warren D, et al. Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. Journal of Cellular Immunotherapy 2016;2:59-68.
8. A Cure for Cancer? How CAR-T Therapy is Revolutionizing Oncology. Available at https://labiotech.eu/car-t-therapy-cancer-review/ [Last accessed 24 Nov 2017].
9. Food and Drug Administration. FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574154.htm [Last accessed 27 Nov 2017].
10. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Science translational medicine 2011;3:95ra73-95ra73.
11. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor–modified T cells in chronic lymphoid leukemia. New England Journal of Medicine 2011;365:725-733.
12. Children with Cancer UK. Acute Lymphoblastic Leukaemia. Available at: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/acute-lymphoblastic-leukaemia/ [Last accessed 14 Nov 2017].
13. Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood 2008;111:5515-23.
14. Reinfjell T, Lofstad GE, Nordahl HM, et al. Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. Eur J Cancer Care (Engl) 2009;18:364-70.
15. Jones BL. The challenge of quality care for family caregivers in pediatric cancer care, In Seminars in oncology nursing, Elsevier, 2012.
16. Tarr J, Pickler RH. Becoming a cancer patient: a study of families of children with acute lymphocytic leukemia. Journal of Pediatric Oncology Nursing 1999;16:44-50.
17. 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 14 Feb 2018].
18. American Cancer Society. Acute Lymphocytic Leukemia. Available at: https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html [Last accessed 23 Jan 2018].
19. American Cancer Society. Chronic Lymphocytic Leukemia. Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html [Last accessed 23 Jan 2018].
20. Ravandi F, Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009;23:1043-63, vi.

21. 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 14 Nov 2017].
22. 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 14 Feb 2018].
23. Cancer Research UK. About acute lymphoblastic leukaemia. Available at: http://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [Last accessed 14 Nov 2017].
24. NHS choices. Acute lymphoblastic leukaemia. Available at: https://www.nhs.uk/Conditions/Leukaemia-acute-lymphoblastic/Pages/Introduction.aspx#symptoms [Last accessed 14 Nov 2017].
25. Dana-Farber Boston Children's Cancer and Blood Disorders Center. Relapsed Acute Lymphoblastic Leukemia (ALL). Available at: http://www.danafarberbostonchildrens.org/conditions/leukemia-and-lymphoma/relapsed-acute-lymphoblastic-leukemia.aspx [Last accessed 14 Nov 2017].
26. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62:61-73.
27. 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.
28. Pui C-H, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. Journal of Clinical Oncology 2015;33:2938-2948.
29. Nebraska Hematology-Oncology. 2016. Available at: http://yourcancercare.com/types-of-cancer/leukemia/childhood-acute-lymphoblastic-leukemia/childhood-acute-lymphoblastic-leukemia-refractory [Last accessed 15 Feb 18].
30. 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. Journal of clinical oncology 2009;28:648-654.
31. 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.
32. Mody R, Li S, Dover DC, et al. Twenty-five–year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood 2008;111:5515-5523.
33. Reinfjell T, Lofstad G, Nordahl H, et al. Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. European journal of cancer care 2009;18:364-370.
34. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Journal of Clinical Oncology 2006;24:1917-1923.
35. 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. Journal of Clinical Oncology 2016;34:4381-4389.
36. 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. Pediatric blood & cancer 2014;61:1088-1093.
37. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence by age. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-One [Last accessed 14 Nov 2017].
38. Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2016;27:v69-v82.
39. NCCN Guidelines: Acute Lymphoblastic Leukemia Version 1. 2017. Available at: https://www.nccn.org/patients/guidelines/all/files/assets/common/downloads/files/all.pdf [Last accessed 27 Nov 2017].
40. Macmillan Cancer Suport. Hyper-CVAD chemotherapy. Available at: https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/combinationregimen/hyper-cvad.aspx [Last accessed 1st Feb 2018].

41. ALLR3: An International Collaborative Trial for Relapsed and Refractory ALL. Available at: http://journals.plos.org/plosone/article/file?type=supplementary&id=info:doi/10.1371/journal.pone.0108107.s003 [Last accessed 14 Feb 2018].
42. European Medicines Agency (EMA). EVOLTRA (clofarabine) 1 mg/ml concentrate 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/000613/WC500031191.pdf [Last accessed 17 May 2018].
43. European Medicines Agency (EMA). 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: 27 Feb 2018].
44. NICE. TA450: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. Available at: https://www.nice.org.uk/guidance/ta450. [Last accessed 27 Feb 2018] 2017.
45. Commissioning Medicines for Children in Specialised Services Reference: NHS England: 170001/P. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf [Last accessed 17 May 2018].
46. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-847.
47. 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.
48. 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.
49. 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.
50. 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.
51. Lee DW, Stetler-Stevenson M, Yuan CM, et al. Long-term outcomes following CD19 CAR T cell therapy for B-ALL are superior in patients receiving a fludarabine/cyclophosphamide preparative regimen and post-CAR hematopoietic stem cell transplantation: Am Soc Hematology, 2016.
52. Maude S, Teachey D, Rheingold S, et al. Durable remissions after monotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children and young adults with relapsed/refractory ALL, In Haematologica, FERRATA STORTI FOUNDATION VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY, 2016.
53. Maude SL, Barrett DM, Rheingold SR, 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.
54. 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.
55. 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.
56. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. Crit Care Med 2017;45:e124-e131.
57. Clinicaltrials.gov ELIANA (NCT02435849). Available at: https://clinicaltrials.gov/ct2/show/NCT02435849 [Last accessed 30th Jan 2018].
58. Clinicaltrials.gov ENSIGN (NCT02228096). Available at: https://clinicaltrials.gov/ct2/show/NCT02228096 [Last accessed 30th Jan 2018].
59. Clinicaltrials.gov B2101J (NCT01626495). Available at: https://clinicaltrials.gov/ct2/show/NCT01626495?term=PEDI-CART&rank=1 [Last accessed 30th Jan 2018].

60. 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.
61. 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.
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 (Supplementary Appendix; 30th January 2017 data cut-off). Data on File. 2017.
63. 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.
64. 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 Feb 18]. .
65. 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. Data on File. 2016.
66. Campana D. Minimal residual disease in acute lymphoblastic leukemia. ASH Education Program Book 2010;2010:7-12.
67. 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.
68. 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.
69. 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.
70. 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.
71. 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.
72. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D: Springer, 2014.
73. 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.
74. Novartis Pharmaceuticals UK Ltd. Feedback from UK expert clinicians. 2018.
75. Locatelli F, Zugmaier G, Vora A, et al. Blinatumomab use in pediatric patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) from an open-label, multicenter, expanded access study: American Society of Clinical Oncology, 2017.
76. 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 7 Feb 2018].
77. 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 7 Feb 2018].
78. 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.
79. 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.
80. Phillippo DM, Ades AE, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from http://www.nicedsu.org.uk. [Last accessed: 4 February 2018].
81. NICE. ID893: Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10091. [Last accessed 26 Apr 2018].

82. pCODR final economic guidance report: Blinatumomab (Blincyto) for pediatric acute lymphoblastic leukemia. pCODR. 2017.
83. Chimeric Antigen Receptor T-Cell Therapy for B Cell Cancers: Effectiveness and Value. Institute for Clinical and Economic Review (ICER). 2017.
84. 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.
85. Snider J, Brauer M, Hao Y, et al. The Economic Value of CTL019 Therapy for Pediatric Patients with Relapsed and Refractory Acute Lymphoblastic Leukemia in the United Kingdom: Am Soc Hematology, 2017.
86. Hao Y, Eldjerou LK, Yang H, et al. Cost-Effectiveness Analysis of CTL019 for the Treatment of Pediatric and Young Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia in the United States: Am Soc Hematology, 2017.
87. 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.
88. 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.
89. National Institute for Health and Care Excellence. TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta306. [Last accessed: 16 November 2017].
90. 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.
91. NHS Network Site Specific Group (NSSG) - Haematology. Myeloid Group - FLA-IDA. 2017; http://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-9-fla-ida.pdf. Last accessed: January 2018.
92. Amgen Europe B.V. BLINCYTO 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: 27 Feb 2018].
93. 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.
94. 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: 08 February 2018].
95. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21:2175-97.
96. ISPOR Estimating the Long-Term Outcomes Associated With ImmunoOncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Available at: https://www.ispor.org/valueoutcomesspotlight_long-term-immuno-oncology-therapies_January-February_2018.pdf [Last accessed May 2018].
97. 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].
98. Office for national statistics. Interim Life Tables: England & Wales Period expectation of life based on data for the years 2014-2016. Last accessed [March 2018].
99. 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.
100. 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.

101. 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.
102. 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.
103. 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.
104. 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;376:2009-17.
105. Bertaina A, Vinti L, Strocchio L, et al. The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukaemia of childhood. British journal of haematology 2017;176:629-636.
106. 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.
107. EQ-5D-Y (Youth). https://euroqol.org/eq-5d-instruments/eq-5d-y-about/. Last accessed: April 2018.
108. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
109. 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.
110. 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.
111. Maziarz RT, Guerin A, Gauthier G, et al. Five-Year Direct Cost of Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) Undergoing Allogeneic Stem Cell Transplantation (HSCT): An Analysis from US Payers' Perspective: Am Soc Hematology, 2015.
112. Maziarz RT, Guérin A, Gauthier G, et al. Five-year direct costs of acute lymphoblastic leukemia pediatric patients undergoing allogeneic stem cell transplant. International Journal of Hematologic Oncology 2016;5:63-75.
113. Lehne M, Hickstein L, Salimullah T, et al. Costs of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL)-an Analysis of German Claims Data: Am Soc Hematology, 2016.
114. Department of Health. NHS Reference Costs 2016-2017. National schedule of reference costs: the main schedule. Available: https://www.gov.uk/government/publications/nhs-reference-costs-2016-to-2017. Accessed March 2016.
115. Drugs and pharmaceutical electronic market information (eMIT). https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Last accessed: April 2018.
116. British National Formulary (BNF) Online. Available at: https://bnf.nice.org.uk/. Last accessed [30th Apr 2018].
117. Haabeth OAW, Tveita AA, Fauskanger M, et al. How do CD4+ T cells detect and eliminate tumor cells that either lack or express MHC class II molecules? Frontiers in immunology 2014;5.
118. Martínez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells?: AACR, 2015.
119. 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: http://www.nicedsu.org.uk [Last accessed: 20 Nov 2017].
120. National Institute for Health and Care Excellence. Exploring the assessment and appraisal of regenerative medicines and cell therapy products. Available at: https://www.nice.org.uk/about/what-we-do/science-policy-research/nice-research. [Last accessed: 24 Aug 2017].
121. 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.
122. National Cancer Institute (NCI) Dictionary of Cancer Terms. Philadelphia chromosome. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44179 [Last accessed 27 Nov 2017].

123. UK Stem Cell Strategy Oversight Committee. Unrelated Donor Stem Cell Transplantation in the UK: Effective Affordable Sustainable. NHS: Blood and Transplant. 2014.
124. Hospital and community health services (HCHS) index. Available at: https://www.pssru.ac.uk/pub/uc/uc2017/sources-of-information.pdf. Last accessed [24 Apr 2018].
125. 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].
126. 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.
127. British National Formulary (BNF) Online: RoActemra (tocilizumab) 80mg/4mL. Available at: https://bnf.nice.org.uk/medicinal-forms/tocilizumab.html Last accessed [17 Apr 2018]. .
128. Maude S, Grupp S, Pulsipher M, et al. Analysis of safety data from 2 multicenter trials of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-all), In Haematologica, FERRATA STORTI FOUNDATION VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY, 2017.
129. Monthly Index of Medical Specialities (MIMS). Available at: http://www.mims.co.uk/drugs/. Last accessed [Aug 2017].
130. 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 [17 Apr 2018]. .
131. Ren S, Minton J, Whyte S, et al. A New Approach for Sampling Ordered Parameters in Probabilistic Sensitivity Analysis. Pharmacoeconomics 2018;36:341-347.

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Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years
[ID1167]

Dear Novartis

The Evidence Review Group, York Centre for Reviews and Dissemination and the technical team at NICE have looked at the submission received on 18th May from Novartis. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** 29th June 2018. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Victoria Kelly, Technical Lead (Victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (Stephanie.callaghan@nice.org.uk).

Yours sincerely

Frances Sutcliffe
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Trial data

A1. **Priority question**: The data used in the analyses presented in the company submission and used in the model are based on the following data cuts: ELIANA 31st Dec 2017; ENSIGN 6th Oct 2017; and, B2101J 30th Jan 2017. If a more recent data cut is available, please update all survival analyses (overall survival (OS) and event-free survival (EFS)), by providing updated Kaplan-Meier curves, numbers of events/N, median values, 95% confidence intervals (CIs) and p-values (i.e. update figures 21-22 on pages 65-66 .

A2. **Priority question:** Please provide, if available, the full clinical study reports (CSR's) with the later data cut-off for both the ELIANA (31st Dec 2017) and the ENSIGN (6th Oct 2017) trials.

Trial population

A3. **Priority question**: Please provide, if available, the baseline characteristics for the full intention-to-treat (ITT) population (i.e. including patients who did not receive infusion) from the latest data cut of the ENSIGN, ELIANA and B2101J trials.

A4. **Priority question:** Approximately 16% of patients in the ENSIGN, ELIANA and B2101J trials received an allogenic stem cell transplant (allo-SCT) following infusion with tisagenlecleucel**.**

a) Please provide the proportion of patients receiving allo-SCT for each trial separately.

b) Given that tisagenlecleucel is given with curative intent please comment on the rates of allo-SCT observed in the ENSIGN, ELIANA and B2101J trials and the company's expectations regarding the use of allo-SCT in the UK to consolidate tisagenlecleucel induced remission.

A5. Please provide the number of patients, if any, with Philadelphia chromosome positive (PH+ve) disease in the ENSIGN, ELIANA and B2101J trials

A6. Please provide the number of patients with 0,1,2,3 or more relapses in the ENSIGN, ELIANA and B2101J trials.

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A7. Please provide a CONSORT flow diagram for the full ITT population for each trial. 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.

Trial design

A8. Please provide details of the descriptive statistics median (range), mean (SD) on the average time from enrolment to infusion in the ENSIGN, and B2101J trials.

A9. The ELAINA CSR suggests considerable variability in the time between enrolment and infusion (range 30 to 105 days). Please comment on why there is such variability and the factors contributing to this.

A10. The median time between enrolment and infusion in the ELAINA CSR is reported as 45 days. This is substantially longer than the 3 to 4 weeks estimated in the company submission. Please comment on this discrepancy and why you consider that manufacturing time will be substantially shorter if tisagenlecleucel is introduced into UK practice.

Survival Outcomes

A11. **Priority question**: Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival, and overall survival by:

- Karnofsky/Lanksy performance status [(>=90 vs <90],
- response status ORR at 3 months [Yes, No],
- complete response [CR] at 3 months [Yes, No] and
- whether the patient received HSCT after infusion with tisagenlecleucel-T [Yes, No].

A12. **Priority question**: Please provide Kaplan-Meier curves for time to B-cell recovery in patients achieving complete remission (CR) or complete remission with incomplete blood count recovery (CRi) from the B2101J and ENSIGN trials, and from the latest data cut of ELIANA trial.

A13. **Priority question**: Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for patients enrolled in the ENSIGN, ELIANA and B2101J trials, but who were not successfully infused with tisagenlecleucel.

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A14. **Priority question**: Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for the ENSIGN, ELIANA and B2101J trials, starting at enrolment date, rather than date of infusion.

A15. **Priority question**: Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for all clofarabine and clorafabine combination trials as listed on page 68, Table 19, either separately and/or with data pooled across trials.

A16. Please provide Kaplan-Meier plots of overall survival for the B2101J trial with censoring for allo-SCT.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question:** Please provide a scenario analysis within the economic model based on a subgroup analysis of ELAINA, ENSIGN and BJ2101J that excludes patients with primary refractory disease.

B2. **Priority question:** Please provide an additional scenario analysis in which the efficacy of fludarabine, cytarabine and idarubicin (FLA-IDA) is estimated for each of the trials reported on page 68, Table 19 either separately or with data pooled across trials. Please provide this analysis using both mixture cure model (MCM) and simple parametric extrapolation. If this is not feasible please prioritise including the Hijiya et al (2011) and Locatelli et al (2009) trials separately in the economic model**.**

B3. **Priority question:** The estimate cure fraction based on the MCM analysis of EFS suggests quite different cure fractions to those estimated based on OS. Please comment on the reported differences in the size of the cure fraction between EFS and OS and provide an explanation for these differences.

Infrastructure and process issues

B4. **Priority question:** Please provide further details on the process of administration, tracking and shipping of apheresis products and the management of severe toxicity. In response to this question please refer to the recent article by Perica et al[1] and summarise whether similar processes are likely to be required within the NHS, highlighting any additional resource/cost implications that have not been formally quantified (e.g. training costs, additional administration costs associated with ensuring the chain of custody of the cell product, whether ITU beds may need to be made available even if not used etc).

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[1]Reference: *Karlo Perica, Kevin J. Curran, Renier J. Brentjens, Sergio A. Giralt, Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Products at Memorial Sloan Kettering Cancer Center, Biology of Blood and Marrow Transplantation (2018),* https://doi.org/10.1016/j.bbmt.2018.02.018*).*

B5. Please provide further information concerning the process for obtaining the separate certification and batch release appropriate to the European regulations governing genetically modified advanced therapy medicinal products.

B6. Please provide additional evidence to support the expected time to supply an infusible product for European patients.

Adverse events

B7. **Priority question:** Leukapheresis-related AEs were not included in the model. Please update the model, to include disutility associated with incidence of leukapheresis-related AEs.

B8. **Priority question**: Please report additional descriptive statistics e.g. median (interquartile range and range), mean (SD, SE) on the duration of ICU stay caused by cytokine release syndrome (CRS) from ELAINA, ENSIGN and BJ2101J.

B9. Given the uncertainty surrounding the potential duration of intravenous immunoglobulin (IVIG) treatment, please present additional scenario analyses assuming a duration of 0 months and a lifetime.

B10. Given that in the UK IVIG is used only in people with recurrent infections caused by B-cell aplasia/hypogammaglobulinaemia, with prophylaxis as standard practice, the 73.33% rate used in the trial is potentially conservative. Please provide a scenario in line with UK practice, factoring in non-IVIG prophylaxis costs if possible.

Resource use

B11. **Priority question**: It is anticipated that leukapheresis products will be taken from patients and cryo-preserved until they are needed. Please produce a scenario analysis including these costs (see B-cell Lymphoma model).

B12. **Priority question**: Please include a scenario analysis in which treatment and care costs associated with grade 1 and 2 CRS events are included in the model.

B13. **Priority question**: Please confirm that the payment for tisagenlecleucel-T is only made for people who are successfully infused.

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Section C: Textual clarifications and additional points

No questions

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Single technology appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years
[ID1167]

Dear Frances,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group. We thank the team for their comments on the submission and hope that our responses to the individual questions in turn below provide clarity for our approach in the submission and the necessary additional information where this has been possible.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed. Accompanying these response letters is also a zipped folder data package, containing the references referred to within this response.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

[redacted]

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Section A: Clarification on effectiveness data

Trial data

A1. **Priority question**: The data used in the analyses presented in the company submission and used in the model are based on the following data cuts: ELIANA 31st Dec 2017; ENSIGN 6th Oct 2017; and, B2101J 30th Jan 2017. If a more recent data cut is available, please update all survival analyses (overall survival (OS) and event-free survival (EFS)), by providing updated Kaplan-Meier curves, numbers of events/N, median values, 95% confidence intervals (CIs) and p-values (i.e. update figures 21-22 on pages 65-66.

The data cut-offs included in the submission represent the most recent data available to Novartis for the ELIANA, ENSIGN and B2101J clinical trials. The Kaplan-Meier plots and survival analyses included within the submission and economic model therefore cannot be updated further at this time.

New data are expected to become available in July 2018 for the ELIANA trial and Q3-4 2018 for the B2101J trial.

A2. **Priority question:** Please provide, if available, the full clinical study reports (CSRs) with the later data cut-off for both the ELIANA (31st Dec 2017) and the ENSIGN (6th Oct 2017) trials.

The latest CSR for ENSIGN (6th Oct 2017 data cut-off) will be available in July 2018. For ELIANA, no full CSR is being developed for the latest data cut-off (31st Dec 2017).

The data tables from the latest ELIANA (31st Dec 2017) and ENSIGN (6th Oct 2017) data cut-offs used to inform the submission are therefore included in a zipped folder data package accompanying this response.

Trial population

A3. **Priority question**: Please provide, if available, the baseline characteristics for the full intention-to-treat (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 full ITT population (i.e. the enrolled set, including patients who did not receive infusion), where available, from the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017 data cut-offs, respectively) are presented below.

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Table 1: Patient baseline characteristics for the full ITT population in ELIANA, ENSIGN and B2101J

Characteristic	ELIANA (N=97)	ENSIGN (N=73)	B2101J (N=66)[a]
Demographics			
Age (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Mixed Ethnicity	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	
Weight for tisagenlecleucel manufacturing (kg)[b]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]
Karnofsky/Lanksy performance status, n (%)			
100	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	-
50	[redacted]	[redacted]	-
<50	[redacted]	[redacted]	-
Missing	[redacted]	[redacted]	[redacted]
Disease history and prior therapies			
Diagnosis of disease, n (%)			
B-cell ALL	[redacted]	[redacted]	[redacted]
T-cell ALL	[redacted]	[redacted]	[redacted]
Age at initial diagnosis (years)			

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

[a] Data for B2101J presented in this submission refer to the non-CNS3 ALL cohort only. [b] Data not available for all patients, hence why n numbers are less than the total enrolled set. [c] Calculated for relapsed patients only
Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system; ITT: intention-to-treat; MRD: minimal residual disease; N/A: not applicable; NR: not reported; SCT: stem cell transplantation; SD: standard deviation.
Source: ELIANA Data on File (31st Dec 2017); ENSIGN Data on File (6th Oct 2017); B2101J Data on File (30th Jan 2017).[1-3]

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A4. **Priority question:** Approximately 16% of patients in the ENSIGN, ELIANA and B2101J trials received an allogenic stem cell transplantation (allo-SCT) following infusion with tisagenlecleucel**.**

a) Please provide the proportion of patients receiving allo-SCT for each trial separately.

The proportions of patients who received an allo-SCT following infusion with tisagenlecleucel in the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017 data cut-offs, respectively) are presented below.

Table 2: Number of subsequent allo-SCTs received in ELIANA, ENSIGN and B2101J

	ELIANA (N=79)	ENSIGN (N=58)	B2101J (N=56)	Total (N=193)
Number of subsequent allo-SCT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: allo-SCT: allogeneic stem cell transplantation.
Source: ELIANA Data on File (31st Dec 2017); ENSIGN Data on File (6th Oct 2017); B2101J Data on File (30th Jan 2017).[1-3]

b) Given that tisagenlecleucel is given with curative intent please comment on the rates of allo-SCT observed in the ENSIGN, ELIANA and B2101J trials and the company's expectations regarding the use of allo-SCT in the UK to consolidate tisagenlecleucel induced remission.

It is fully anticipated that tisagenlecleucel will be given with curative intent in UK clinical practice. This is also the anticipation of the UK clinical experts consulted as part of this appraisal, who commented that the rate of [redacted] of patients receiving a subsequent allo-SCT is an overestimate of likely UK clinical practice.[4] A reason for this is that initially some physicians in the US chose to consolidate with an allo-SCT following infusion with tisagenlecleucel; however, this is no longer considered an appropriate option whilst patients are in remission. If a patient suffers a relapse following tisagenlecleucel infusion, a subsequent allo-SCT is theoretically an option, but UK expert clinician feedback is that the number of people who would be candidates for a subsequent allo-SCT at this stage would be negligible.

A5. Please provide the number of patients, if any, with Philadelphia chromosome positive (Ph+ve) disease in the ENSIGN, ELIANA and B2101J trials

The proportion of patients with Ph+ve B-cell ALL in the ELIANA and ENSIGN clinical trials (31st Dec 2017 and 6th Oct 2017 data cut-offs, respectively) is presented below. In the B2101J clinical trial (30th Jan 2017 data cut off), no cytogenetic testing was mandated in the study protocol, therefore only limited cytogenetic data were available at baseline. In the non-CN3 cohort, the Philadelphia chromosome status was unknown in [redacted] patients, negative in [redacted] patients and [redacted] patients. Therefore, the exact proportion of patients with Ph+ve B-cell ALL is not available.

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Table 3: Proportion of patients with Ph+ve B-cell ALL in ELIANA, ENSIGN and B2101J

	ELIANA (N=79)	ENSIGN (N=58)	B2101J (N=56)
Ph+ve patients, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: Ph+ve: Philadelphia chromosome positive; NR: not reported.
Source: ELIANA Data on File (31st Dec 2017); ENSIGN Data on File (6th Oct 2017); B2101J Data on File (30th Jan 2017).[1-3]

A6. Please provide the number of patients with 0,1,2,3 or more relapses in the ENSIGN, ELIANA and B2101J trials.

Descriptive statistics for the number of patients with previous relapses in ELIANA (31st Dec 2017) and ENSIGN (6th Oct 2017) are provided below. The exact number of patients with 0, 1, 2 or ≥3 relapses was not available.

Table 4: Number of relapses prior to tisagenlecleucel infusion in ELIANA and ENSIGN

Number of relapses	ELIANA (N=79)	ENSIGN (N=58)
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]

Abbreviations: SD: standard deviation.
Source: ELIANA Data on File (31st Dec 2017); ENSIGN Data on File (6th Oct 2017).[1, 3]

The number of patients with 0, 1, 2 or ≥3 relapses in B2101J (30th Jan 2017) is presented below.

Table 5: Number of relapses prior to tisagenlecleucel infusion in B2101J

Number of relapses	B2101J (N=56)
0	[redacted]
1	[redacted]
2	[redacted]
≥3	[redacted]

Source: B2101J Data on File (30th Jan 2017).[2]

A7. Please provide a CONSORT flow diagram for the full ITT population for each trial. 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.

CONSORT diagrams summarising the patient flow from screening to enrolment in the ELIANA, ENSIGN and B2101J clinical trials are presented below. In the ELIANA clinical trial (31st Dec 2017 data cut-off), 113 patients were screened and 97 were enrolled. Reasons for exclusion following screening

[redacted].[3]

In the ENSIGN clinical trial (6th Oct 2017 data cut-off),

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[redacted].[1]

In the B2101J clinical trial (30th Jan 2017 data cut-off), screening of [redacted]. In addition to screening failure, patients with CNS3 ALL and lymphoma were excluded from the enrolled set.[2]

Figure 1: CONSORT diagram of patient flow (ELIANA)

[redacted]

Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 2: CONSORT diagram of patient flow (ENSIGN)

[redacted]

Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 3: CONSORT diagram of patient flow (B2101J)

[redacted]

Abbreviations: ALL: acute lymphoblastic leukaemia; CNS: central nervous system.
Source: B2101J Data on File (30th Jan 2017).[2]

Trial design

A8. Please provide details of the descriptive statistics median (range), mean (SD) on the average time from enrolment to infusion in the ENSIGN, and B2101J trials.

The descriptive statistics on time from enrolment to tisagenlecleucel infusion in the ENSIGN and B2101J clinical trials (6th Oct 2017 and 30th Jan 2017 data cut-offs, respectively) are presented below.

Table 6: Time from enrolment to tisagenlecleucel infusion in ENSIGN and B2101J

Time since enrolment to tisagenlecleucel infusion	ENSIGN (N=58)	B2101J (N=56)
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]

Abbreviations: SD: standard deviation.
Source: ENSIGN Data on File (6th Oct 2017); B2101J Data on File (30th Jan 2017).[1, 2]

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A9. The ELIANA CSR suggests considerable variability in the time between enrolment and infusion (range 30 to 105 days). Please comment on why there is such variability and the factors contributing to this.

Factors influencing the time between enrolment and tisagenlecleucel infusion were investigated in the JULIET trial of adults with DLBCL. It is anticipated that these factors translate to the variability in the time between enrolment and infusion in the ELIANA clinical trial (25th Apr 2017). However, recent data have been published that demonstrate median throughput time from receipt of leukapheresis material to return of tisagenlecleucel product to treatment site was 23 days, and the range was 21–37 days, highlighting the already reduced variability in turnaround time.

The main driver of the turnaround time from leukapheresis to infusion in the JULIET clinical trial was the availability of manufacturing capacity relative to demand. Early in the study conduct, there were limited manufacturing slots available, but also fewer sites and consenting patients. As more clinical sites on-boarded many more patients consented; however, manufacturing capacity had not yet increased and only the Novartis Morris Plains manufacturing site in the US was actively producing tisagenlecleucel. This is reflected in the time from leukapheresis to infusion, which peaked in the second quartile of the study, as patients who signed consent waited for available manufacturing capacity. Although capacity at the Morris Plains manufacturing facility steadily increased between Dec-2015 and Aug-2016, the additional capacity needed to be applied to an existing queue of patients who had signed informed consent. In August 2016, the EU manufacturing site (Fraunhofer) started to actively produce tisagenlecleucel, and, albeit to a moderate extent, supported the overall reduction in the size of the manufacturing queue. By the end of the study, after several months at high capacity, the total time from leukapheresis to infusion again declined as the queue was drawn down.

A second driver of the turnaround time was the potential for delays between leukapheresis and the start of manufacturing. The Novartis manufacturing process for tisagenlecleucel uses cryopreserved leukapheresis as starting material. The time of leukapheresis collection can therefore be decoupled from the time of product manufacture for up to 9 months, which was the shelf life of leukapheresis at the time of JULIET. Furthermore, JULIET accepted cryopreserved leukapheresis collected outside of the pivotal study protocol under a separate apheresis protocol or on the physician's discretion. The use of cryopreserved leukapheresis allowed patients to be leukapheresed prior to enrolment based on local leukapheresis availability and the patient's clinical situation. The measurement of time from leukapheresis to infusion may be more relevant for CAR-T products manufactured from fresh apheresis, which cannot be stored for extended periods prior to manufacturing. For the Novartis product manufactured from cryopreserved cells, the length of time from leukapheresis to infusion in the JULIET trial included storage time when using previously collected leukapheresis, any waiting time for manufacturing capacity, and time after manufacture is completed for a patient to be medically stabilised in case required. It is worth noting that in both the ELIANA and JULIET trials, enrolment of patients occurred following successful screening. The apheresis product then entered a queue for manufacture. In contrast, in other CAR-T therapy trials, enrolment occurred after successful screening and confirmation of an available manufacturing slot. It is therefore

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considered that ELIANA and JULIET are more analogous to the real-world setting and manufacturing capacity has been substantially increased in order to supply real world demand which does not wait for confirmation of manufacturing slots. Recent data have been published on the throughput time for a total of 37 commercial patient orders (for B-ALL) that were placed for tisagenlecleucel.[5] Median throughput time for the 37 commercial batches from receipt of leukapheresis material and required documentation at the manufacturing facility to return of tisagenlecleucel product to treatment site was 23 days, and the range was 21–37 days, highlighting the already reduced variability in turnaround time.

A10. The median time between enrolment and infusion in the ELIANA CSR is reported as 45 days. This is substantially longer than the 3 to 4 weeks estimated in the company submission. Please comment on this discrepancy and why you consider that manufacturing time will be substantially shorter if tisagenlecleucel is introduced into UK practice.

As described in the response to Clarification Question A9 above, the main driver of the turnaround time from leukapheresis to infusion in the ELIANA clinical trial was the availability of manufacturing capacity relative to demand. At the beginning of the ELIANA clinical trial, demand outweighed capacity and therefore patients experienced a longer duration between enrolment and infusion.

Several incremental changes to the manufacturing process have been implemented to help standardise the production, and thus directly impact total manufacturing, QC testing, and release time. Key changes have included decreasing the time from cell product harvest to release, decreasing the time for batch record review, decreasing the number and impact of deviations, and streamlining deviation investigations.

Recent data have been published on the throughput time for a total of 37 commercial patient orders (for B-ALL) that were placed for tisagenlecleucel.[5] All 37 orders were processed to completion, met all specified release criteria, and were successfully supplied with commercial tisagenlecleucel products (cut-off date, 30th January 2018).[5] Median throughput time for the 37 commercial batches from receipt of leukapheresis material and required documentation at the manufacturing facility to return of tisagenlecleucel product to treatment site was 23 days (range, 21–37 days). For the batch with the 37-day throughput time, a laboratory error in the quality control part of testing and disposition was detected, which prevented timely release of the manufactured batch.[5]

These published data correspond to the prespecified manufacturing time of 3–4 weeks in the SmPC and quoted in the submission. Ongoing refinements are expected to further decrease the throughput time from receipt of leukapheresis material to return of manufactured product to 21 days. Therefore, within clinical practice in the UK, it is expected that manufacturing time will be reduced compared to the median time reported in the ELIANA CSR (45 days) hence the assumption of 21 days of manufacturer time adopted as part of the base case analysis of the submission.

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Survival Outcomes

A11. Priority question: Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival, and overall survival by:

- Karnofsky/Lanksy performance status [(>=90 vs <90],
- response status ORR at 3 months [Yes, No],
- complete response [CR] at 3 months [Yes, No] and
- whether the patient received HSCT after infusion with tisagenlecleucel-T [Yes, No].

Given the economic model is based on EFS and OS data, Novartis have assumed that this question is meant to request EFS data rather than PFS data here.

Kaplan-Meier curves (with the number of patients at risk at each time point) for EFS and OS by Karnofsky/Lanksy performance status, response status ORR at 3 months, CR at 3 months and whether the patient received allo-SCT after infusion with tisagenlecleucel are provided below for the ELIANA (31st Dec 2017 data cut-off), ENSIGN (6th Oct 2017 data cut-off) and B2101J (30th Jan 2017) clinical trials.

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

[redacted]

Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 5: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by baseline Karnofsky/Lansky performance status (≥90 vs <90) by IRC assessment in ENSIGN

[redacted]

Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 6: Kaplan-Meier curve for EFS by baseline Karnofsky/Lansky performance status (≥90 vs <90) in B2101J

[redacted]

Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: B2101J Data on File (30th Jan 2017).[2]

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Figure 7: 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: ELIANA Data on File (31st Dec 2017).[3]

Figure 8: Kaplan-Meier curve for OS (without censoring for allo-SCT) by baseline Karnofsky/Lansky performance status (≥90 vs <90) by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; IRC: independent review committee; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 9: Kaplan-Meier curve for OS by baseline Karnofsky/Lansky performance status (≥90 vs <90) in B2101J

Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival.
Source: B2101J Data on File (30th Jan 2017).[2]

Figure 10: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by best overall response at 3 months by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; IRC: independent review committee; NE: not estimable; NR: not reported; SCT: stem cell transplantation; UNK: unknown.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 11: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by best overall response at 3 months by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; IRC: independent review committee; NE: not estimable; NR: not reported; SCT: stem cell transplantation; UNK: unknown.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 12: Kaplan-Meier curve for EFS by best overall response in B2101J

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; NE: not estimable; NR: not reported; UNK: unknown.
Source: B2101J Data on File (30th Jan 2017).[2]

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Figure 13: Kaplan-Meier curve for OS by best overall response at 3 months by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable; NR: not reported; OS: overall survival; SCT: stem cell transplantation; UNK: unknown.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 14: Kaplan-Meier curve for OS by best overall response at 3 months by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable; NR: not reported; OS: overall survival; UNK: unknown.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 15: Kaplan-Meier curve for OS by best overall response in B2101J

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; NE: not estimable; NR: not reported; OS: overall survival; UNK: unknown.
Source: B2101J Data on File (30th Jan 2017).[2]

Figure 16: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by best overall response at 3 months (CR vs CRi vs UNK/NR) by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; CR; complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; IRC: independent review committee; NE: not estimable; NR: not reported; SCT: stem cell transplantation; UNK: unknown.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 17: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by best overall response at 3 months (CR vs CRi vs UNK/NR) by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; CR; complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; IRC: independent review committee; NE: not estimable; NR: not reported; SCT: stem cell transplantation; UNK: unknown.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 18: Kaplan-Meier curve for EFS by best overall response (CR vs CRi vs UNK/NR) in B2101J

Abbreviations: CI: confidence interval; CR; complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; NE: not estimable; NR: not reported.
Source: B2101J Data on File (30th Jan 2017).[2]

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Figure 19: Kaplan-Meier curve for OS by best overall response at 3 months (CR vs CRi vs UNK/NR) by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; CR; complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable; NR: not reported; OS: overall survival; SCT: stem cell transplantation.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 20: Kaplan-Meier curve for OS by best overall response at 3 months (CR vs CRi vs UNK/NR) by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable; NR: not reported; OS: overall survival; SCT: stem cell transplantation; UNK: unknown.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 21: Kaplan-Meier curve for OS by best overall response (CR vs CRi vs UNK/NR) in B2101J

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; NE: not estimable; NR: not reported; OS: overall survival.
Source: B2101J Data on File (30th Jan 2017).[2]

Figure 22: Kaplan-Meier curve for EFS (without censoring for allo-SCT) by whether received post-infusion allo-SCT (Yes vs No) 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: ELIANA Data on File (31st Dec 2017).[3]

Figure 23: Kaplan-Meier curve for EFS (without censoring for allo-SCT) whether received post-infusion allo-SCT (Yes vs No) by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 24: Kaplan-Meier curve for EFS whether received post-infusion allo-SCT (Yes vs No) in B2101J

Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable; SCT: stem cell transplantation.
Source: B2101J Data on File (30th Jan 2017).[2]

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Figure 25: Kaplan-Meier curve for OS by whether received post-infusion allo-SCT (Yes vs No) by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; IRC: independent review committee; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: ELIANA (31st Dec 2017).[3]

Figure 26: Kaplan-Meier curve for OS whether received post-infusion allo-SCT (Yes vs No) by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; IRC: independent review committee; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 27: Kaplan-Meier curve for OS whether received post-infusion allo-SCT (Yes vs No) in B2101J

Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: B2101J Data on File (30th Jan 2017).[2]

A12. **Priority question:** Please provide Kaplan-Meier curves for time to B-cell recovery in patients achieving complete remission (CR) or complete remission with incomplete blood count recovery (CRi) from the B2101J and ENSIGN trials, and from the latest data cut of ELIANA trial.

Kaplan-Meier curves for time to B-cell recovery in patients achieving CR or CRi from the ELIANA and ENSIGN clinical trials (31st Dec 2017 and 6th Oct 2017 data cut-offs, respectively) are provided below. Unfortunately, time to B-cell recovery data were not collected in the B2101J clinical trial and hence cannot be presented here.

Figure 28: Kaplan-Meier curve for time to B-cell recovery in peripheral blood in patients who achieved CR or CRi by IRC assessment in ELIANA

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 29: Kaplan-Meier curve for time to B-cell recovery in peripheral blood in patients who achieved CR or CRi by IRC assessment in ENSIGN

Abbreviations: CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IRC: independent review committee; NE: not estimable.
Source: ENSIGN Data on File (6th Oct 2017).[1]

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A13. Priority question: Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for patients enrolled in the ENSIGN, ELIANA and B2101J trials, but who were not successfully infused with tisagenlecleucel.

Kaplan-Meier curves (with the number of patients at risk at each time point) for EFS and OS for the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017, respectively), for patients who were enrolled but not successfully infused with tisagenlecleucel are provided below.

Figure 30: Kaplan-Meier curve for EFS (censoring allo-SCT) by IRC assessment for patients not successfully infused with tisagenlecleucel in ELIANA

Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 31: Kaplan-Meier curve for EFS (censoring allo-SCT) by IRC assessment for patients not successfully infused with tisagenlecleucel in ENSIGN

Abbreviations: CI: confidence interval; EFS: event-free survival; IRC: independent review committee; NE: not estimable; SCT: stem cell transplantation.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 32: Kaplan-Meier curve for EFS for patients not successfully infused with tisagenlecleucel in B2101J

Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: B2101J Data on File (30th Jan 2017).[2]

Figure 33: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel in ELIANA

Abbreviations: CI: confidence interval; OS: overall survival; SCT: stem cell transplantation.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 34: 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: ENSIGN Data on File (6th Oct 2017).[1]

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Figure 35: Kaplan-Meier curve for OS for patients not successfully infused with tisagenlecleucel in B2101J

Abbreviations: CI: confidence interval; CNS: central nervous system; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: B2101J Data on File (30th Jan 2017).[2]

A14. Priority question: Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for the ENSIGN, ELIANA and B2101J trials, starting at enrolment date, rather than date of infusion.

Kaplan-Meier curves (with the number of patients at risk at each time point) for EFS and OS for the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017, respectively), starting at enrolment date, rather than date of infusion are provided below.

Figure 36: Kaplan-Meier curve for EFS from enrolment in ELIANA

Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 37: Kaplan-Meier curve for EFS from enrolment in ENSIGN

Abbreviations: CI: confidence interval; EFS: event-free survival; NE: not estimable.
Source: ENSIGN Data on File (6th Oct 2017).[1]

Figure 38: Kaplan-Meier curve for EFS from enrolment in B2101J

Abbreviations: CI: confidence interval; CNS: central nervous system; EFS: event-free survival; NE: not estimable.
Source: B2101J Data on File (30th Jan 2017).[2]

Figure 39: Kaplan-Meier curve for OS from enrolment in ELIANA

Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival.
Source: ELIANA Data on File (31st Dec 2017).[3]

Figure 40: Kaplan-Meier curve for OS from enrolment in ENSIGN

Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival.
Source: ENSIGN Data on File (6th Oct 2017).[1]

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Figure 41: Kaplan-Meier curve for OS from enrolment in B2101J

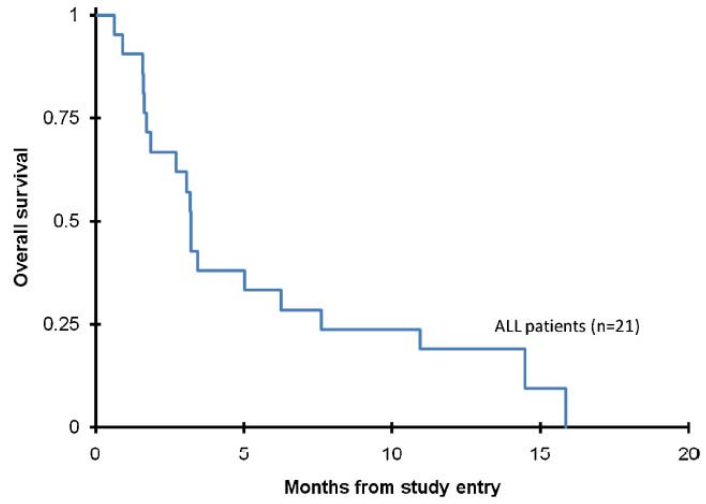
[redacted]

Abbreviations: CI: confidence interval; CNS: central nervous system; NE: not estimable; OS: overall survival.
Source: B2101J Data on File (30th Jan 2017).[2]

A15. **Priority question:** Please provide, if available, the Kaplan-Meier curves (with the number of patients at risk at each time point) for event free survival, and overall survival for all clofarabine and clofarabine combination trials as listed on page 68, Table 19, either separately and/or with data pooled across trials.

The Kaplan-Meier curves for EFS were not available for Miano *et al.* (2012), Hijiya *et al.* (2011), Locatelli *et al.* (2009), Cooper *et al.* (2013), Messinger *et al.* (2012) or Jeha *et al.* (2006). The OS Kaplan-Meier curves from each of the clofarabine and clofarabine combination trials are provided below.

Figure 42: Kaplan-Meier curve for overall survival from Cooper *et al.* (2013)



Source: Cooper *et al*. (2013).[6]

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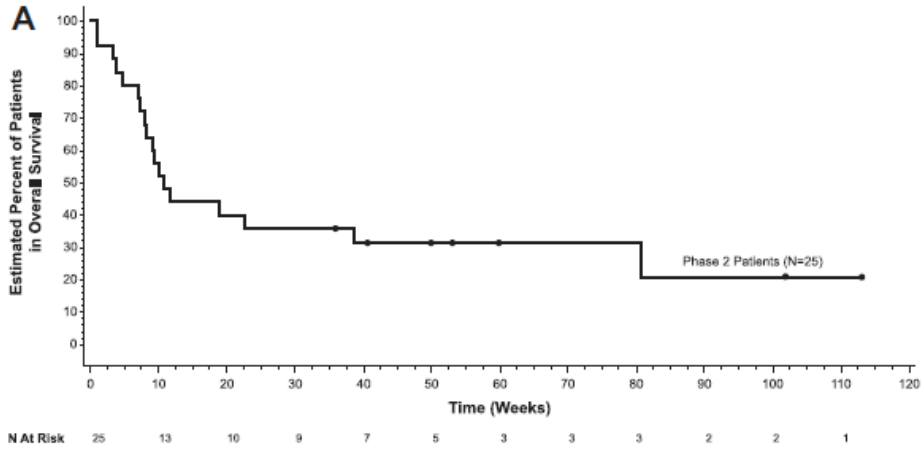
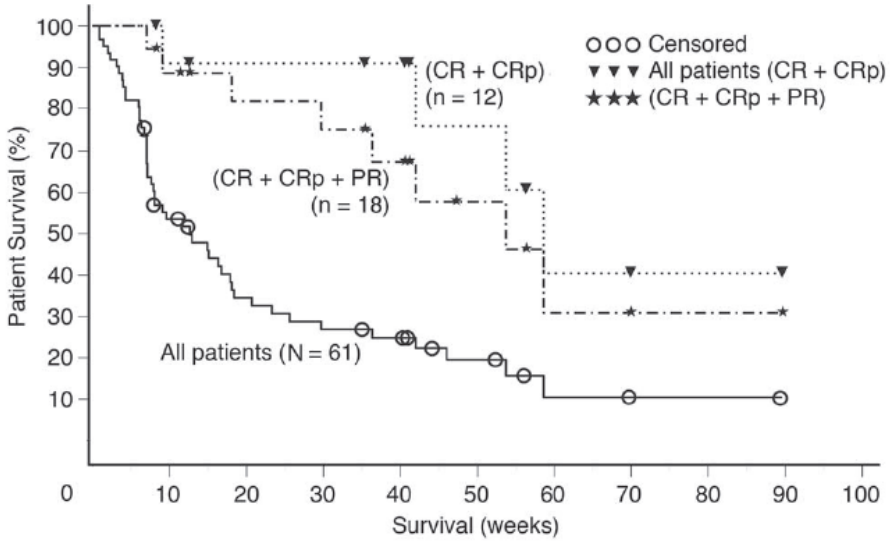
Figure 43: Kaplan-Meier curve for overall survival from Hijiya *et al*. (2011)



Source: Hijiya *et al*. (2011).[7]

Figure 44: Kaplan-Meier curve for overall survival from Jeha *et al*. (2006)



Source: Jeha *et al*. (2006).[8]

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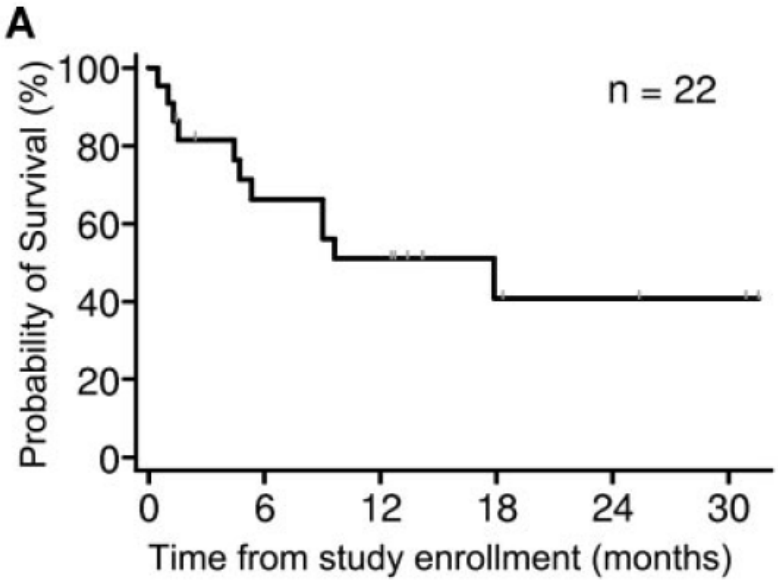
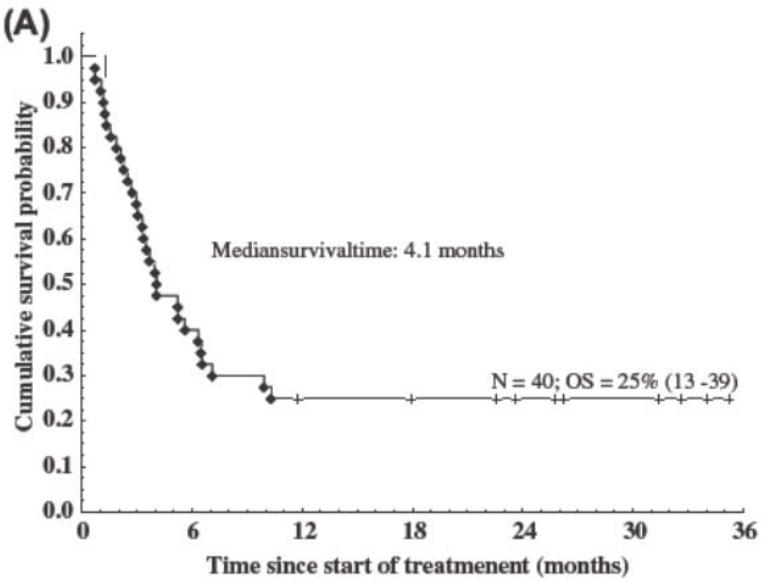
Figure 45: Kaplan-Meier curve for overall survival from Messinger *et al.* (2012)



Source: Messinger *et al.* (2012).[9]

Figure 46: Kaplan-Meier curve for overall survival from Miano *et al.* (2012)



Source: Miano *et al.* (2012).[10]

A16. Please provide Kaplan-Meier plots of overall survival for the B2101J trial with censoring for allo-SCT.

The Kaplan-Meier curve of OS for the B2101J trial censoring for allo-SCT is provided below.

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Figure 47: Kaplan-Meier curve of OS from B2101J with censoring for allo-SCT

Abbreviations: CI: confidence interval; CNS: central nervous system; NE: not estimable; OS: overall survival; SCT: stem cell transplantation.
Source: B2101J Data on File (30th Jan 2017).[2]

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question:** Please provide a scenario analysis within the economic model based on a subgroup analysis of ELIANA, ENSIGN and BJ2101J that excludes patients with primary refractory disease.

It should be noted that patients with primary refractory disease are included within the anticipated licensed indication for tisagenlecleucel and therefore it would be not considered appropriate to exclude these patients from the cost-effectiveness analysis.

However, the results of a scenario analysis excluding patients with primary refractory disease is presented below for tisagenlecleucel at both list price and PAS price, respectively. A total of [redacted], [redacted] and [redacted] patients were removed across ELIANA, ENSIGN, and B2101J, respectively. A mixture cure model approach has been adopted in line with the submission base case; the curve choices have been selected following the same process as detailed in our submission, based on clinical plausibility, visual fit and statistical fit (AIC).

The results demonstrate that the exclusion of patients with primary refractory disease has little effect on the base case ICERs.

Table 7: Scenario analysis excluding patients with primary refractory disease (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Excluding patients with primary refractory disease (Mixture cure model approach OS: Loglogistic; EFS: Gompertz)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Table 8: Scenario analysis excluding patients with primary refractory disease (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Excluding patients with primary refractory disease (Mixture cure model approach OS: Loglogistic; EFS: Gompertz)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,416
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,407

Abbreviations: AIC: Akaike information criterion; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years.

B2. **Priority question:** Please provide an additional scenario analysis in which the efficacy of fludarabine, cytarabine and idarubicin (FLA-IDA) is estimated for each of the trials reported on page 68, Table 19 either separately or with data pooled across trials. Please provide this analysis using both mixture cure model (MCM) and simple parametric extrapolation. If this is not feasible please prioritise including the Hijiya et al (2011) and Locatelli et al (2009) trials separately in the economic model.

In response to this question, Novartis have prioritised providing scenario analyses that include the Hijiya *et al.* (2011) and Locatelli *et al.* (2009) trials separately in the economic model as a proxy for the efficacy of FLA-IDA. These scenarios can be selected on the "Specification tab" of the updated model accompanying this response. The resulting cost-effectiveness results, both using the simple parametric extrapolation and mixture cure model approaches are presented below in Table 9 (with tisagenlecleucel at list price) and Table 10 (with tisagenlecleucel at PAS price). The curve choices have been selected following the same process as detailed in our submission, based on clinical plausibility, visual fit and statistical fit (AIC).

It should be noted that the use of the mixture cure model approach is not considered appropriate for salvage chemotherapy for the reasons detailed in the submission. Clinical expert feedback was clear that the majority of patients in relapse post-transplantation 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. The cure fractions and long-term survival extrapolations predicted using the mixture cure model approach explored for the submission were considered too optimistic by UK clinical experts, and therefore standard parametric models were used for the base case to model OS with salvage chemotherapy. This was also the case here: for Locatelli *et al.* (2009) the cure rates predicted by each of the models were between 7.0–20.0%

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and therefore the lognormal was chosen with a cure rate of 8.9% as being, amongst other factors, one of the most clinically plausible options. For Hijiya *et al.* (2011]), the cure rates predicted by each of the models were all clinically implausible (e.g. ranging from 17.0–22.5%). Therefore, the scenarios based on the mixture cure model approach for salvage chemotherapy presented below may be overestimating the efficacy of salvage chemotherapy and the ICERs should be interpreted with extreme caution.

Table 9: FLA-IDA efficacy source scenario analyses (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Salvage chemotherapy efficacy from Hijiya *et al.* (2011) (Standard parametric survival approach OS: Weighted using AIC; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Salvage chemotherapy efficacy from Hijiya *et al.* (2011) (Mixture cure model approach OS: Loglogistic; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Salvage chemotherapy efficacy from Locatelli et al. (2009) (Standard parametric survival approach OS: Lognormal; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Salvage chemotherapy efficacy from Locatelli *et al.* (2009) (Mixture cure model approach OS: Lognormal; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Table 10: FLA-IDA efficacy source scenario analyses (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: Salvage chemotherapy efficacy from Hijiya *et al.* (2011) (Standard parametric survival approach OS: Weighted using AIC; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,615
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,361
Scenario: Salvage chemotherapy efficacy from Hijiya *et al.* (2011) (Mixture cure model approach OS: Loglogistic; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,883
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,038
Scenario: Salvage chemotherapy efficacy from Locatelli et al. (2009) (Standard parametric survival approach OS: Lognormal; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,371
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,544
Scenario: Salvage chemotherapy efficacy from Locatelli *et al.* (2009) (Mixture cure model approach OS: Lognormal; EFS: based on OS)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,590
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,277

Abbreviations: AIC: Akaike information criterion; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PAS: patient access scheme; QALYs: quality-adjusted life years.

B3. **Priority question:** The estimate cure fraction based on the MCM analysis of EFS suggests quite different cure fractions to those estimated based on OS. Please comment on the reported differences in the size of the cure fraction between EFS and OS and provide an explanation for these differences.

In the base case economic analysis, the estimated cure rate from the OS MCM is [redacted], whereas the estimated cure rate from the EFS MCM is [redacted], based on the selected extrapolations. It is therefore not considered that the cure fractions for OS and EFS are very different.

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EFS in the tisagenlecleucel trials 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 MCM refers to the proportion of patients who do not have disease-related death, whereas the cure rate estimated from EFS MCM refers to the proportion of patients who do not have disease-related events and 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. The base case cure rates are similar, contributing to the plausibility of the base case extrapolation choices ([redacted] for OS and [redacted] for EFS).

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 MCM models do not fit the EFS curve as well as the OS curves. 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.

Infrastructure and process issues

B4. **Priority question:** Please provide further details on the process of administration, tracking and shipping of apheresis products and the management of severe toxicity. In response to this question please refer to the recent article by Perica et al[1] and summarise whether similar processes are likely to be required within the NHS, highlighting any additional resource/cost implications that have not been formally quantified (e.g. training costs, additional administration costs associated with ensuring the chain of custody of the cell product, whether ITU beds may need to be made available even if not used etc).

[1]Reference: *Karlo Perica, Kevin J. Curran, Renier J. Brentjens, Sergio A. Giralt, Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Products at Memorial Sloan Kettering Cancer Center, Biology of Blood and Marrow Transplantation (2018),* https://doi.org/10.1016/j.bbmt.2018.02.018*).*

The shortlist of clinical sites to be commissioned by NHSE for the administration of tisagenlecleucel has been based on the site service specification and JACIE 6.01 or JACIE 7 accreditation. Previous CAR-T therapy clinical trial experience has also been considered. Taken together, it is anticipated that the only sites that Novartis will onboard will already have the facilities, skills and processes in place for the administration of tisagenlecleucel. From the engagement that Novartis has to date with several sites this is indeed the case. The only additional requirements will be training on the Novartis ordering system and the safety training as required by EMA (which will be provided by Novartis). As such, this training will require attendance from prescribing clinicians, nurses and ICU staff, the cost of which has not been included within the base case analysis. It is not anticipated that ICU beds will need to be routinely reserved. Therefore, beyond the training time, there are no further resource/cost implications anticipated by Novartis that have not been considered.

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B5. Please provide further information concerning the process for obtaining the separate certification and batch release appropriate to the European regulations governing genetically modified advanced therapy medicinal products.

Tisagenlecleucel can be manufactured either in the EU at the Fraunhofer Institut für Immunologie und Zelltherapie (Leipzig, Germany) or at the Novartis Morris Plains facility (New Jersey, USA). It is foreseen that tisagenlecleucel will be produced from either site for EU patients. For medicinal products imported from third countries, retesting of each batch within the EEA upon importation would normally be required in compliance with Eudralex Volume 4 Annex 16 1.5.4. Therefore, in principle testing should be performed in the EU upon shipping. However, the Morris Plains site will manufacture and test the product in compliance with EU regulations related to manufacturing facility design, in accordance with the Eur. Ph. / EU specific requirements where applicable, and in accordance with the EU marketing authorisation. Certification will be carried out after shipping the product batch to the EU by the Novartis Qualified Person in Nuremberg (Germany) in accordance with Article 51(1) of Directive 2001/83/EC.

B6. Please provide additional evidence to support the expected time to supply an infusible product for European patients.

As described in our response to Question A10 above, several incremental changes to the manufacturing process have been implemented to help standardise the production, and thus directly impact total manufacturing, QC testing, and release time. Key changes have included decreasing the time from cell product harvest to release, decreasing the time for batch record review, decreasing the number and impact of deviations, and streamlining deviation investigations.

Recent data have been published on the throughput time for a total of 37 commercial patient orders (for B-ALL) that were placed for tisagenlecleucel.[5] All 37 orders were processed to completion, met all specified release criteria, and were successfully supplied with commercial tisagenlecleucel products (cut-off date, 30th January 2018).[5] Median throughput time for the 37 commercial batches from receipt of leukapheresis material and required documentation at the manufacturing facility to return of tisagenlecleucel product to treatment site was 23 days (range, 21–37 days). For the batch with the 37-day throughput time, a laboratory error in the quality control part of testing and disposition was detected, which prevented timely release of the manufactured batch.[5]

Therefore, these published data correspond to the prespecified manufacturing time of 3–4 weeks in the SmPC and quoted in the submission.

Adverse events

B7. **Priority question:** Leukapheresis-related AEs were not included in the model. Please update the model, to include disutility associated with incidence of leukapheresis-related AEs.

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The AEs included in the economic model cover grade 3 or 4 AEs experienced in ≥5% of patients. Data on the grade 3 or 4 AEs experienced by any patient within 2 days of the leukapheresis procedure in the ELIANA trial are presented below (these data were not available for the ENSIGN and B2101J trials). Altogether, [redacted], hence none of the AEs were experienced in ≥5% of patients. Given each leukapheresis-related grade 3 or 4 AE was experienced by only [redacted] patients enrolled in the ELIANA trial, the inclusion of any disutility associated with the incidence of leukapheresis-related AEs was not considered appropriate in the submission. Furthermore, no disutility data are available from the trial to capture any reduction in utility from AEs related to leukapheresis. Therefore, the model has not been updated to include disutility associated with the incidence of leukapheresis-related AEs in response to this question.

Table 11: Adverse events started within 2 days of the leukapheresis procedure in ELIANA

Adverse event	Duration	Grade
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: ELIANA Data on File (31st Dec 2017).[3]

B8. **Priority question**: Please report additional descriptive statistics e.g. median (interquartile range and range), mean (SD, SE) on the duration of ICU stay caused by cytokine release syndrome (CRS) from ELIANA, ENSIGN and B2101J.

The duration of Intensive care unit (ICU) stay, and accompanying descriptive statistics, for the treatment of CRS in the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017 data cut offs, respectively) is presented below.

Table 12: Duration of ICU stay due to CRS in ELIANA, ENSIGN and B2101J

Duration of ICU stay due to CRS (days)	ELIANA (N=79)	ENSIGN (N=58)	B2101J (N=56)[a]
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]

[a] Data from B2101J is for CRS post-tisagenlecleucel infusion period at Day 28 for non-CNS3 ALL patients.
Abbreviations: CRS: cytokine release syndrome; ICU: intensive care unit; SD: standard deviation.
Source: ELIANA Data on File (31st Dec 2017); ENSIGN Data on File (6th Oct 2017); B2101J Data on File (30th Jan 2017).[1-3]

B9. Given the uncertainty surrounding the potential duration of intravenous immunoglobulin (IVIG) treatment, please present additional scenario analyses assuming a duration of 0 months and a lifetime.

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The results of a scenario assuming an IVIG duration of 0 months are presented in Table 13 (tisagenlecleucel at list price) and Table 14 (tisagenlecleucel at PAS price), respectively.

Feedback from eight UK clinical experts consulted in response to this question was that a lifetime duration of IVIG is totally clinically implausible and therefore we have not presented this scenario here. UK clinical expert feedback was that the duration of IVIG treatment would typically be aligned with the duration of B-cell aplasia; given the estimate of 11.4 months used in the base case of our submission is based on the time to B-cell recovery, this duration is considered to represent the most appropriate duration of IVIG in this indication and therefore to assume a lifetime duration of IVIG treatment is completely inappropriate.

Table 13: Scenario analysis assuming a duration of IVIG of 0 months (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case analysis							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: assuming a duration of 0 months of IVIG treatment							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; IVIG: intravenous immunoglobulin; LYG: life years gained; QALYs: quality-adjusted life years.

Table 14: Scenario analysis assuming a duration of IVIG of 0 months (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case analysis							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: assuming a duration of 0 months of IVIG treatment							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,359
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,956

Abbreviations: ICER: incremental cost-effectiveness ratio; IVIG: intravenous immunoglobulin; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

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B10. Given that in the UK IVIG is used only in people with recurrent infections caused by B-cell aplasia/hypogammaglobulinaemia, with prophylaxis as standard practice, the [redacted] rate used in the trial is potentially conservative. Please provide a scenario in line with UK practice, factoring in non-IVIG prophylaxis costs if possible.

Further feedback from UK clinical experts has been sought to answer this question, who stated that the [redacted] of patients receiving IVIG in the ELIANA trial as assumed in the base case of our submission is appropriate and a reasonable assumption. As such, no further scenarios have been conducted here.

Resource use

B11. **Priority question**: It is anticipated that leukapheresis products will be taken from patients and cryo-preserved until they are needed. Please produce a scenario analysis including these costs (see B-cell Lymphoma model).

As in the economic model for DLBCL, the cost of cryopreservation in the treatment of B-cell ALL is assumed to be negligible and is therefore set to zero. Thus, a scenario analysis including this cost would have no effect on the base case analysis presented within the submission and has not been presented here.

B12. **Priority question**: Please include a scenario analysis in which treatment and care costs associated with grade 1 and 2 CRS events are included in the model.

In the base case analysis, [redacted] developed CRS at Grade 3/4 and were therefore considered to accrue the costs of treatment for CRS within the economic model. When also taking into account patients who developed CRS at Grade 1/2 from the ELIANA, ENSIGN and B2101J clinical trials (31st Dec 2017, 6th Oct 2017 and 30th Jan 2017 data cut-offs, respectively; [redacted] patients overall experienced CRS at Grade 1–4.[1-3]

Results from a scenario analysis incorporating the costs associated with CRS for patients with CRS at Grade 1–4 are provided below, with tisagenlecleucel provided at list price in Table 15, and with the confidential PAS discount in Table 16. It has been assumed that patients with Grade 1 or 2 CRS accrue the same costs of treatment as those with Grade 3 or 4 CRS. This is an extremely conservative assumption given patients with Grade 1 or 2 CRS would not be admitted to ICU or treated with tocilizumab in UK clinical practice. Nevertheless, as shown in Table 16 below, the inclusion of costs associated with CRS for patients with CRS at Grade 1–4 has minimal impact on the overall cost-effectiveness results.

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Table 15: Scenario analysis using including the cost of treating CRS at Grade 1 or above (tisagenlecleucel list price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case analysis							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: including the cost of treating CRS at Grade 1–4							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 16: Scenario analysis using including the cost of treating CRS at Grade 1 or above (tisagenlecleucel PAS price)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Base case analysis							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Scenario: including the cost of treating CRS at Grade 1–4							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,161
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,420

Abbreviations: CRS: cytokine release syndrome; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

B13. **Priority question**: Please confirm that the payment for tisagenlecleucel-T is only made for people who are successfully infused.

Yes, it can be confirmed that the payment for tisagenlecleucel is only made for people who are successfully infused. Invoices will be issued to the treatment centre when they accept receipt of tisagenlecleucel into the treatment centre.

However, the following abbreviated cancellation, replacement and credit policy will be in place such that no centre would be charged if the patient was not infused with tisagenlecleucel for the reasons set out below:

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Order Cancellation

If the treatment centre has ordered tisagenlecleucel but has not yet accepted receipt, the following terms on cancellation apply.

A treatment centre may file a cancellation request for tisagenlecleucel that has been ordered by it or on its behalf to Novartis prior to receipt of tisagenlecleucel in accordance with the cancellation process. Novartis will not charge for the cost of a validly cancelled tisagenlecleucel order.

Product replacement or credit

After receipt of the tisagenlecleucel, the treatment centre can request replacement or a credit in accordance with the terms as defined below.

If the specific circumstances set forth below render tisagenlecleucel unusable, the treatment centre may request replacement product or a credit. Novartis will determine, in its sole discretion, whether replacement product can be provided (if replacement product is available) or issue a credit; except that in the case of unusable product replacement or credit requests that result from the deterioration of the patient's performance status or patient death.

Novartis, in its sole discretion, will provide replacement tisagenlecleucel (if replacement product is available) or issue a credit for unusable product under the following circumstances:

1. Treatment centre human error renders tisagenlecleucel unsuitable for infusion, provided that the treatment centre has used best efforts to comply with the Prescribing Information as approved by the applicable regulatory authority and any other requirements for the handling and administration of tisagenlecleucel.
2. Tisagenlecleucel temperature excursions at the treatment centre, provided that the treatment centre has used best efforts to comply with the Prescribing Information as approved by the applicable regulatory authority and any other requirements for the handling and administration of the product.
3. Tisagenlecleucel damaged during shipment but not recognised until after receipt at the treatment centre. The treatment centre must also call the Novartis Customer Service Centre to complete a Product Quality Complaint.
4. Tisagenlecleucel temperature excursion during transportation but not recognised until after receipt at the treatment centre. The treatment centre must also call the Novartis Customer Service Centre to complete a Product Quality Complaint.
5. Product quality issue identified at any point after receipt but prior to infusion. The treatment centre must also call the Novartis Customer Service Centre to complete a Product Quality Complaint.

Subject to the credit request process being followed, Novartis will issue a credit for unusable product under the following circumstances:

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6. Tisagenlecleucel has expired before it can be administered to the patient in accordance with the approved Prescribing Information and any Novartis instructions for product use. Credit request must be submitted within 30 days of product expiration. Note, Novartis may, in its sole discretion, reject credit requests where delays in administering the product are due solely to treatment centre protocols that differ from the approved Prescribing Information or other Novartis instructions for product use.
7. After tisagenlecleucel is received by the treatment centre, but before infusion, a physician determines and certifies that, in his/her independent clinical judgement, the prescribed patient's performance status has deteriorated to a point where tisagenlecleucel can no longer be safely administered to the patient.
8. Patient death prior to infusion.

Section C: Textual clarifications and additional points

No questions

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References

1. Novartis Pharmaceuticals UK Ltd. Data on File. ENSIGN 6th October 2017 cut-off date.
2. Novartis Pharmaceuticals UK Ltd. Data on File. B2101J 30th January 2017 cut-off date.
3. Novartis Pharmaceuticals UK Ltd. Data on File. ELIANA 31st December 2017 cut-off date.
4. Novartis Pharmaceuticals UK Ltd. Feedback from UK clinical experts. 2018.
5. Majors B, Spencer T, Ericson S, et al. European Hematology Association (EHA) 2018, Poster Presentation: Initial Experience in US Commercial Manufacturing of Tisagenlecleucel, a Chimeric Antigen Receptor (CAR)-T Cell Therapy for Paediatric Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia. Abstract available at: https://learningcenter.ehaweb.org/eha/2018/stockholm/215467/brian.majors.initial.experience.in.us.commercial.manufacturing.of.html?f=menu=6*ce_id=1346*ot_id=19055*media=3*marker=167 [Last Accessed 22 June 2018].
6. 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;60:1141-7.
7. 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.
8. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Journal of Clinical Oncology 2006;24:1917-1923.
9. 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;120:285-90.
10. Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma 2012;53:1693-8.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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 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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Bloodwise
3. Job title or position	Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Bloodwise's mission is to beat all blood cancers – stopping people from dying, improving the lives of everyone affected by blood cancer, and where possible preventing people getting blood cancer in the first place. We do this by funding world leading research, supporting all those affected by blood cancer, and campaigning for improvements in care and services. We are entirely funded by voluntary donations and have approximately 100 members of staff and 140 patient ambassadors plus many more volunteers and supporters.
4b. 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?	As CAR-T cell therapy is so new and the majority of the clinical trials so far have taken place outside the UK, it has been very difficult to track down patients to assist us with our submission. This is also more challenging when the patients involved are children. In preparing our submission for the other appraisal of tisagenlecleucel-T (for treating relapsed or refractory diffuse large B-cell lymphoma (ID1166)), we initially sent an email to our database of patient ambassadors asking them to contact us to share their experiences of diffuse large B-cell lymphoma (DLBCL) and CAR-T cell therapy. They in turn contacted other members of the blood cancer community both within the UK and outside who they thought might be able to help but this did not lead anywhere. We also consulted our medical advisory panel, an expert group of clinicians, to gain further insight into the condition and patients' experiences using this treatment from a clinical perspective.

	Fortunately, one of the clinicians we consulted was able to put us in touch with a colleague running a CAR-T academic trial for treatment of DLBCL in London. She then put us in touch with a colleague working on another CAR-T academic trial for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL). This clinician arranged for us to speak to one of the participants of the trial, a 19 year old ALL patient, so we carried out an in depth interview with him covering all aspects of his treatment, the outcome and his views on his experiences. We also spoke to the patient's mother who is his main carer and separately to the aforementioned clinicians. Our submission is based on these responses (although both the patient and clinicians are not named in the submission).
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Common symptoms of ALL include tiredness caused by anaemia, bruising and bleeding, infections and weight loss. Other symptoms include swollen lymph nodes, stomach and bone pain, night sweats and generally feeling unwell. If is most common in children and young people. The patient we spoke to describes how he struggled with extreme tiredness and lost a lot of weight. When he was diagnosed in Autumn 2016, he was at school, studying for his A-Levels and the tiredness and effects of treatment made attending school difficult. He started a treatment plan of chemotherapy that was due to last for 3 years and had the treatment for a few months during which time he suffered from severe side effects including vomiting, fatigue and infections. This involved travelling from his home in Essex into central London once or twice a week and then returning to school the following day which was a huge challenge for him.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The patient we spoke to had chemotherapy for several months which was not effective. He was then was advised that he needed a bone marrow transplant. He underwent more intensive chemotherapy to prepare for the transplant. The chemotherapy caused the side effects outlined above – sickness, fatigue, high fevers and these were more severe during the more intensive treatment, which was also more onerous as required greater attendance at hospital. He had the transplant in May 2017 and his recovery was a long and slow process. However, he made a full recovery and spent several months cancer free when he was able to continue with his studies and get on with his life. A few months later, he unfortunately relapsed and no other conventional treatment options were available to him so his treating consultant suggested that he participate in the CAR-T trial at UCLH, essentially as a last resort.
8. Is there an unmet need for patients with this condition?	Yes. The unmet need here is for treatment that offers patients a better chance of achieving remission where traditional chemotherapy has failed. Our patient witness and his mother describe how the clinical trial and treatment gave them hope at a time when all his other options had failed and that although the treatment is intensive, requiring several weeks' stay in hospital/hospital accommodation and a short course of intensive chemotherapy (therefore not removing the need for chemotherapy entirely) the therapy is over relatively quickly and it motivated him to see his rapid improvement following treatment. One of the clinicians we spoke to, who is leading on another CAR-T trial (for treatment of relapsed or refractory DLBCL), also highlighted that where patients do not respond to more than one line of therapy, their options are exceptionally limited. Therefore, although the CAR-T therapy is not guaranteed to work, it offers these patients another chance so any response is positive and furthermore, when it does work, the results in trials to date have been "fantastic" with those patients that respond well achieving full remission.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As stated above, the most significant advantage is that the treatment offers those patients who have failed to respond to one or more previous therapies another chance. Response rates in ALL trials have been exceptionally good according to the clinicians we have spoken to and where a response is made, the results have been remarkable. Our patient witness felt that the CAR-T therapy had less side effects than chemotherapy and reported that he did not feel as unwell during treatment. He described the therapy as intense – he had to have a first lower 'dose' initially to check that he could tolerate the process, followed by the full treatment two weeks later, after which he had to remain in the hospital for several weeks. However, it was less draining than chemotherapy as it was over relatively quickly (a few weeks compared to several months of weekly chemotherapy, which he described as seeming to be "never ending"). He also found the treatment better from a psychological point of view as it started to work quickly and within weeks he was cancer free, although he did continue to struggle with infection (as outlined below).
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The treatment is intensive and requires patients to be admitted or stay in ambulatory care close to the hospital for the duration of several weeks which can be difficult when patients and carers have other family responsibilities. Our patient witness' mother explained that this had a big impact on their family life as she has two younger children whom she did not see properly for several weeks. A common side effect is the development of neutropenic sepsis following re-insertion of the engineered cells. The patient is not clear whether he developed this but describes that he was very unwell following reinsertion of the cells for a short period with a high temperature and was briefly admitted to intensive care. However, he was advised from the start that it was likely that he would develop severe side effects so felt well-prepared and reassured by his proximity to the hospital as it meant he received the care he needed very quickly. He underwent treatment at the end of March and has remained in hospital since then as he is still susceptible to infection as his white blood cell count gradually increases, however, it is likely that he will be ready to go home soon. He and his mother advised that the inconvenience of this

	initial period in hospital was insignificant when compared with the possibility that he would respond well to the treatment and ultimately be cancer free.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. What do patients and carers think about using the new technology considering the risk of severe adverse events occurring?	As stated above, as the treatment is being appraised to treat refractory/relapsed disease, this is essentially a last resort option and the patient and carer we spoke to were clear that the potential benefit of achieving a full recovery far outweighed the risk of severe adverse events. They felt that the key thing was being well prepared for this risk and having the reassurance of close proximity to the hospital.
15. What to patients and carers think about the need to remain in close proximity to the treatment centre for 1 month following treatment with the new technology?	See section 14 above. Any inconvenience this caused is far outweighed by the potential for the treatment to work where traditional treatment regimes have failed. Our sources told us that this proximity helped patients deal psychologically with the potential risks of severe adverse reactions to the treatment as they knew they would receive high quality care quickly if they needed it.

16. What do patients and carers think of the extended hospitalisation required during treatment with the new technology?	See section 15 above.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- CAR-T cell therapy is a step-change in the treatment of ALL affecting children and young people and patients should be given access to this innovative treatment.
- The treatment offers children and young people who have run out of options a final chance at achieving a cure.
- Treatment is intensive but short in duration and improvements are seen very quickly which helps patients psychologically.
- A high proportion of patients have responded to treatment in clinical trials and have had exceptionally good results, with most achieving full remission as soon as the treatment has finished.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	Campaigns and Advocacy Director
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also received funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% 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 at: http://www.leukaemiacare.org.uk/wp-content/uploads/2018/02/CODE-OF-PRACTICE.pdf
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information through our support services (helpline, support groups, conferences, communications with our membership) and one to one discussion with patients. This submission is also 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.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. In 2015, there were 832 new cases of acute lymphoblastic leukaemia in the UK. In contrast to most cancer types, approximately 60% of these cases were diagnosed in children and teenagers, with peak incidence being in children aged 0-4 years old. Five-year survival outcomes vary greatly by age, from over 90% in the under 14s to almost 70% in those aged 15-24. However, in the relapsed/refractory setting, survival is significantly reduced with less than 10% of all patients surviving 5 years. **Symptoms** 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%). **Emotional impact** ALL can have a huge 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 survey, two thirds of 16-24 years old reported feeling more depressed or anxious since diagnosis. A diagnosis of childhood ALL can also place huge emotional strain on families and friends. As such, improvements in a patients' treatment and prognosis will also have a wider impact on the lives of their family and friends. **Practical implications** There are also practical impacts of an ALL diagnosis; with 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. **Cost of childhood cancer on families** In our survey, 80% of 16-24-year olds had to reduce their hours in education or employment with the majority having to stop completely (45%). The emotional, practical and financial impacts of having a child diagnosed with ALL are also experienced by the wider family. In 2016, CLIC Sargent published the 'Cancer Costs' report, revealing the average increased monthly expenditure of having a child with cancer was £600, a fifth of parents must take over a year of unpaid leave from work, and three in five accumulate debt as a consequence of their child's cancer. This financial burden leads to 3 in 4 families feeling additional stress and anxiety, during an already difficult time.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	First-line treatment for paediatric ALL has high success rates. However, in the relapsed setting, effective treatment options and survival outcomes are limited. There are currently no guidelines for management of children under the age of 18. Patients often undergo multiple lines of treatment – including chemotherapy, radiation, targeted therapy or stem cell transplant. They may receive FLAG chemotherapy or clofarabine in combination with other agents. This is normally used as a bridge towards stem cell transplant (SCT) for children with relapsed or refractory ALL and have had 2 prior therapies. Tyrosine kinase inhibitors (TKIs) are licensed for use in patients over the age of 18 years old, either alone or in combination with FLAG if they have Philadelphia-chromosome-positive disease. A high-risk indicator in ALL, for which prognosis is poor despite the introduction of TKIs (Leoni and Biondi, 2015). Short term side effects of treatments for childhood ALL can include: fatigue, nausea or sickness, infections, bleeding, organ dysfunction or hair loss. There are also long-term implications of childhood ALL treatment that include loss of fertility or heart damage.

	55% of 16-24 years olds stated that the side effects of their treatment had a large impact, with common side effects being: nausea or vomiting (65%), hair loss (35%), sore mouth (30%), sleeping problems (30%) and weight loss or loss of appetite (25%). Many patients eligible for tisagenlecleucel-T will likely have received at least one SCT during prior treatment. Stem cell transplants are associated with substantial side effects, many outlined above, with the added risk of graft versus host disease (GVHD).
8. Is there an unmet need for patients with this condition?	Current outcomes for relapsed or refractory ALL are poor, demonstrating the clear need for treatments that can achieve and maintain remission for those patients who have exhausted all other options. In the Leukaemia Care survey, improved quality of life and improved/longer survival were the most important features of a new treatment to 16-24-year olds, selected by 85% of respondents. Of the 16-24-year olds who answered the question, 80% said 'yes' when asked if they would be willing to experience additional side effects for a more effective treatment and 56% stated they would like a choice of different treatment options.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	• Potentially lifesaving option for children or young adults who have failed to respond or relapsed following other treatments. • Quick response to treatment for majority of patients – median of 29 days • Only one infusion is necessary for treatment • High response rates to treatment (83% at three months), with all responders achieving MRD negativity. This is associated with positive outcomes and long-term remission. • Improved quality of life with patient reported outcomes showing significantly reduced severity of the practical issues associated with living with ALL e.g. self-care, ability to do daily activities and mobility. • Persistence of Tisagenlecleucel-T in the blood and bone marrow could prevent late relapse.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• Side effects are experienced by a significant number of patients, including neurological toxicities and cytokine release syndrome (CRS) which can be severe or life threatening. • Patients may have concerns over the long-term implications of using genomic editing techniques. • Unknown implications in the persistence of Tisagenlecleucel-T and future pregnancies for women treated.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It appears that clinical characteristics of a patient do not significantly alter the outcome of Tisagenlecleucel-T treatment, therefore, the benefit of treatment could be seen for all ALL patients aged between 3 and 25 years old who have relapsed or refractory disease.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Children and teenagers account for over 60% of the 830 patients diagnosed with acute lymphoblastic leukaemia (ALL) each year in the UK.
- A diagnosis of ALL can have a huge emotional, physical and financial impact on both the patient and their families. For children and young adults this can be a very difficult diagnosis to come to terms and disruptive to their education, early working life and their social learning. Families, also, bear the burden of the diagnosis and time given to caring for the patient.
- Survival for relapsed or refractory ALL is currently very poor, estimated to be around 10% at five years, and for many children and young adults there are limited options if they have failed to respond or relapsed following treatment.
- Tisagenlecleucel-T offers a potentially lifesaving option for children or young adults who have exhausted other options, with very good response rates (83%) and MRD negativity being achieved in all responders in clinical trials.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your organisation's 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 submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists/British Society for Haematology**

3. Job title or position	**Consultant Paediatric Haematologist, Great Ormond Street Hospital, London**
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):
5a. Brief description of the organisation (including who funds it).	Royal College of Pathologists – professional body which sets standards for education and practice in pathology British Society for Haematology – professional membership society representing haematology professionals in the UK
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Cure

or prevent progression or disability.)	
7. 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.)	Initial complete molecular response resulting in long term progression free survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need for around 5-10% of children and young persons with ALL (depending on age and other prognostic variables) who have disease that is unresponsive to conventional therapy including haemopoietic stem cell transplantation.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	First line treatment of children and young people with ALL is highly effective with 80-90% cure rates (depending on age and other prognostic factors) after 2-3 years of treatment with chemotherapy made up of 7 drugs (vincristine, dexamethasone, pegylated asparaginase, anthracyclines, cyclophosphamide, methotrexate and mercaptopurine) given in different combinations during induction, consolidation, CNS directed, interim maintenance, delayed intensification and maintenance phases therapy. These drugs have

	been in use for over 40 years during which there have been no new agents. Yet cure rates have improved by 10%/decade during that period. It's one of the major success stories of modern medicines. However, around 10-15% of patients relapse after first line therapy, around 50% of whom can be cured by re-treatment including haemopoietic stem cell transplantation. The remaining 5-10% of have disease that is "refractory" to conventional therapy and for whom there is an unmet need for new agents.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The vast majority of children and young persons with ALL are treated on clinical trials. The current first line ALL trial, UKALL 2011, is testing ways of reducing the toxicity of treatment whilst retaining efficacy and in the last year of recruitment. There is currently no relapse ALL trial open for this age group in the UK and patients are treated according to a national guideline developed by the childhood leukaemia clinicians network (a specialist interest group of the Childhood Cancer and Leukaemia Group, CCLG). Patients with "refractory" disease as defined in this TA are discussed in a fortnightly national teleconference attended by clinicians from all childhood and young person cancer principle treatment centres (CYP PTC) where guidance as to pathway of care and treatment options are provided to individual clinicians and teams caring for these complex patients.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	See above.
• What impact would the technology have on the current pathway of care?	UK patients already have access to CART therapy through academic studies open at GOSH, UCLH and Manchester. However, capacity is limited and several UK patients have been treated at US centres on a self-pay or crowd funded basis. Availability of licensed, NICE approved CART therapy will remove the need for patients to move abroad for treatment at huge expense and dislocation.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above
• How does healthcare resource use differ between the technology and current care?	The side effect profile of this treatment is different from that of conventional chemotherapy and haemopoietic stem cell transplantation. Clinical teams will need training in recognition and management of these side effects. On the other hand, some side effects associated with conventional chemotherapy will be less frequent or severe and may reduce the need for antibiotics, parenteral nutrition and blood components.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	<5 specialist centres with facilities to safely collect, transfer, receive and infuse cells. The centres should also have access to on site ICU facilities to manage the complications of treatment.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment will be required to expand existing infrastructure for collecting, freezing, transporting and receiving these gene modified cells. Some investment will also be required in creating extra high dependency and intensive care bed capacity.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would only be effective in patients with lymphoblasts that express the CD19 antigen which is the tumour specific target for the cells.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	See above. If there are a limited number of centres delivering the intervention, patients will have to travel and stay for several weeks in the specialist centres.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Also, additional bone marrow and lumbar puncture tests will be required to monitor the efficacy of therapy and persistence of the genetically engineered CART cells. Some of these could be done at local PTCs.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There is no absolute contra-indication to starting therapy although all the clinical trials that tested CARTs had exclusion criteria based on performance status, oxygen requirement, presence of graft-vs-host disease, length of time from HSCT, liver function abnormalities and presence of active bacterial or fungal infection. The treatment is given as a cell infusion in one or two doses, hence stopping treatment is not applicable.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes

16. 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?	The technology is a game changer in the way leukaemia (and possibly other cancers) will be treated in future. Many more such cellular therapy products will come to market in the next few years and the indications are likely to move closer to first line therapy.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	See above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Around 40% of patients experience either cytokine release syndrome (CRS) or neurotoxicity. Depending on the grade of severity, these complications can potentially be life threatening or cause long term disability. Fortunately, the severe grades are rare and can be prevented/managed using an algorithmic approach for intervening with anti-cytokine antibodies such Tocilizumab.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Event-free survival and Overall Survival, both of which were endpoints in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Minimal Residual Disease (MRD) negative remission has been used as a surrogate for EFS and OS and there is evidence that the latter is better in patients who achieve a good MRD response
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Unpublished observations from ongoing academic studies
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Clofarabine is rarely used for refractory ALL nor is FLAG standard of care in this situation in children. The only true comparators are Blinatumomab and Inotuzumab.
21. How do data on real-world experience compare with the trial data?	There is yet no real world experience with this CART product.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	It will be essential to not disadvantage patients on basis of geography if there are only a select few centres chosen to deliver this therapy.

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Game changing technology which serves an unmet need
- Technical challenges to establishing the infrastructure and clinical facilities to deliver the treatment safely will be as much of a challenge as funding it.
- Once established, will improve access to the treatment in the UK and remove the need for patients to go abroad to receive it.
- Long term outcomes remain uncertain as there is insufficient follow-up of patients treated in the clinical trials
- There are no truly valid standard of care comparators as current treatment of this patient group is mostly supportive care and palliation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 3 to 25 years [1167]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor David I. Marks**
2. Name of organisation	**University Hospitals Bristol NHS Trust**

3. Job title or position	**Consultant and Professor of Haematology and Stem cell transplantation**
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? ☐ 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)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. 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	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure refractory ALL that has relapsed or to cure very high risk ALL that is unlikely to be cured by chemotherapy and/or by an allogeneic transplant
8. 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.)	On Eliana, 81% of patients had a complete response and all of these patients were negative for minimal residual disease. Only deep remissions in refractory ALL are associated with a chance of cure and prolonged survival The goal of this sort of high technology, expensive therapy has to be cure
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	I will be confining my statement to the patients I treat and am expert in: the 18-25 year age group with ALL. (Although I know quite a bit about paediatric ALL there are more expert clinicians to advise NICE). There is a clear unmet need in this patient group. Patients who are allografted in this age group and relapse have an extremely poor outcome; the treatment of choice in my opinion is CAR T cells. However, patients who relapse whilst on paediatric inspired chemotherapy also have a very poor outcome with less than 10% surviving long term; this group of patients are also likely to benefit from CAR T cells. In addition there are a small group of patients without rapid access to an allogeneic

	donor (particularly ethnic minorities) and patients unable to have total body irradiation because of pulmonary or cardiac dysfunction
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no clinical guidelines for: 1. Patients who relapse after allogeneic SCT. In general patients can receive blinatumamab with the goal of achieving a CR then either proceeding to second transplant or a CAR T cell trial in the UK or abroad. An alternative is inotuzumab as bridging therapy; this is still being evaluated by NICE, a decision is expected soon. 2. For patients who relapse on chemotherapy the goal is to achieve a CR and to perform an allogeneic transplant. Targeted therapy is the best way of doing this as shown by the Tower and Inovate studies
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In the TYA group there is consensus that patients in first relapse should have therapy to achieve a CR and then an allograft with the best available donor. There is less consensus about the management of post-allograft relapse. Some have the goal of getting the patient to a second transplant, some try to get the patient to CAR T cell therapy and some clinicians only offer palliative therapy of varying intensities
• What impact would the technology have on the current pathway of care?	Briefly, all post allograft relapse would be treated with curative intent ALL patients with early relapse would have an option other than an allograft and/or would have a further curative option if that allograft failed Some patients with slow relapse will avoid targeted therapy and can be controlled with conventional ALL therapy

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	In post allograft relapse CAR T cells would avoid a second transplant which is highly toxic and likely to fail. CAR T cells may require a significant inpatient stay including a 30% chance of a stay in the ITU
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Purely hospitals with specialist experience in managing ALL and all its complications: tertiary referral hospitals and big BMT units
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As NICE will be aware NHSEngland is going to select 2 paediatric and 4 adult first wave providers. These centres will need to demonstrate to JACIE that they have the facilities and experience to administer CAR T cells and its complications (CRS, neurology etc) The first wave centres will not deal with the need so second wave centres will need to follow soon
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	

• Do you expect the technology to increase length of life more than current care?	Yes. On Eliana, the CR rate was 81%, DFS 50% at 12 months, OS 76% and median remission duration not reached at the time of reporting of the Maude NEJM paper
• Do you expect the technology to increase health-related quality of life more than current care?	In certain circumstances CAR T cells will avoid a transplant and will therefore avoid complications such as chronic GVHD that affect QOL Very long term QOL has not been studied in the CAR T cell treated group
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients need to be fit for CAR T cells, able to withstand CRS, have adequate vital organ function. However many patients with refractory ALL are unwell but can undergo this therapy if carefully managed
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Please see the answer to question 13. Patients must have adequate lymphocyte counts (>0.5) and CD3 counts (>0.2) CNS disease should be controlled or in remission

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As with all new therapies there is a learning curve but once that is gone through the therapy can be safely delivered as shown by Eliana in a multicentre multinational setting where the mortality of CRS was zero There needs to be buy in from the hospitals ITU and other ancillary departments eg neurology
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients need to be carefully selected. Patients with very aggressive disease will often not survive the preparation time that is needed. They do not need to be in CR but need to have a reasonable PS Patients' leukaemia cells need to be CD19 positive for this CAR T product
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This technology cures previously incurable patients. It is reasonable to analyse QALYs but there may be a paucity of data in this area and small numbers, and data for the comparator will be lacking. In some settings the comparator does not work and the patient would die rapidly and their quality of life would be very poor

17. 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?	The technology is innovative and can cure new subsets of patients
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, post allograft relapse and very high risk relapse
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The major clinical issues to deal with are severe CRS, neurological complications and longer term cytopenia and hypogammaglobulinaemia Most of these complications impact on QOL on a short term basis but long term follow up is needed

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	This therapy is not available outside clinical trials where the CAR T cells used are different. However, already a significant number of patients are sent overseas or self or crowd fund therapy
• If not, how could the results be extrapolated to the UK setting?	The subset of patients treated on Eliana can be easily extrapolated to the UK
• What, in your view, are the most important outcomes, and were they measured in the trials?	81% MRD negative remissions, 50% PFS at 12 months OS at 12 months of 76% is less significant. Many patients who have active leukaemia will not survive
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not aware of systematic reviews of CAR T cells: it is too early for that
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA450?	The evidence from the inotuzumab evaluation should also be taken into account. This, of course is subject to a post appeal re-evaluation. Of course targeted therapies are not just comparators, they are also ancillary treatments that control the disease enabling CAR T cells to be applied
22. How do data on real-world experience compare with the trial data?	There are no real world data to make this comparison as tisagenlecleucel has only recently been approved by the FDA. It has been used in the US for too short a time for there to be data
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	I am concerned that all ALL patients have access to this therapy and in the case of young adults that there will not be equal access to the very small number of treatment centres giving CAR T cells if this is approved

23b. Consider whether these issues are different from issues with current care and why.	Very different. Nearly all centres can deliver the current care but few will deliver this high tech, high toxicity therapy
Topic-specific questions	
24. Apart from salvage chemotherapy (specifically FLA-IDA [fludarabine, cytarabine and idarubicin]) or blinatumomab are there any other treatments for paediatric and young adult patients up to 25 years?	Yes. In my opinion inotuzumab is the most effective salvage therapy with Inovate showing a 80.7% CR rate with 78.2% being MRD negative.
25. Are TKI's considered relevant to this appraisal?	Yes, CARs work well in Ph pos ALL
26. Would a third TKI be used in clinical practice?	Maybe. Remember NHSEngland does not fund any TKI other than imatinib or ponatinib if the T315I mutation is shown. However some patients manage to access dasatinib or nilotinib
26a. Treatment with CAR T therapy is likely to necessitate	This is conventionally done by the BMT team and by the ITU/HDU staff

prolonged stays in hospital. Who is likely to manage these patients during their time in hospital?	Some hospitals use leukaemia consultants but they are in the minority
26b. Would patients receiving CAR-T cell therapy require additional monitoring to what is currently provided to inpatients?	Yes. Early monitoring for CRS is required shortly after CAR T cell infusions; some of these patients need admission to the ITU. The monitoring in the ITU is not particularly different to other patients
27a. Common side effects of CAR-T therapy are cytokine release syndrome (CRS) and neurotoxicity. Are these events commonly seen in patients in current clinical practice?	The CRS seen with blinatumamab is quite common with bulk disease but is less severe than that seen with CAR T cells CRS is seen after haploidentical transplants where post transplant cyclophosphamide is used
27b. What additional treatment or care (if any) would be given to patients suffering from these adverse events compared to	Tocilizumab was given to 46% of patients in Eliana Some patients required steroids. Some required other IL6 inhibitors

what is provided currently to patients in high dependent units? 27c.Would current clinical staff require additional training and support to manage patients who experience these adverse events?	Yes but this is achievable
28. Would all B-cell aplasia and CRS require additional treatment?	B cell aplasia needs IV immunoglobulin and careful surveillance The treatment of CRS depends on its grading but grade 3-4 CRS needs ITU support, tocilizumab, steroids etc
29. What is the overlap of the fitness criteria for CAR-T treatment and ASCT in people 25 years or under with B-cell ALL?	They are broadly similar Many patients who have had CARs have had an allograft but may be less well than when they had this procedure. A small number of CAR T cell patients require a subsequent allograft. In Eliana it was 7 out of 75

30. What would be the expected relapse rate for patients in remission between 2-5 years after treatment?	Extremely low. Novartis will have more data than I have access to, as will the UPenn groups who have used a similar product for longer.
31. Is it clinically plausible that at 5 years post FLA-IDA approximately 3% of patients would be alive?	This is a vague question. In what clinical setting. In post allograft relapse no patient who had FLAG-Ida will survive long term without further therapy. In first relapse a very occasional patient will survive long term with this chemotherapy alone
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- CAR T cells can cure previously incurable TYA ALL patients. The largest trial shows good 12 month EFS in this clinical setting
- CAR T cells are the therapy of choice in post allograft relapse. Second transplant is to be avoided
- Very long term follow up data are lacking and there are no RCTs. NICE will need to look at the evidence in ways it is not accustomed to doing, and I suspect ICER estimates will be problematic and uncertain
- This therapy can be delivered safely in selected centres, albeit with high short term toxicity
- This therapy must be made available to our patients. If we don't fund it, or delay a decision, wealthy patients/families or those fortunate enough to have crowd funding will go overseas to get this therapy which will be an inequitable, unsatisfactory solution to the problem. I want to see the NICE committee and Novartis work together on this, to find a satisfactory solution and not to adopt adversarial attitudes. There is no precedent to this evaluation: it requires new ways of thinking, from both sides.
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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.

NICE National Institute for Health and Care Excellence

Patient expert statement

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Michael Brandon**

2. Name of organisation	On behalf of Leukaemia Care
3. Job title or position	Project Manager, Pirate Studios
4a. Brief description of the organisation (including who funds it). How many members does it have?	N/A
4b. 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?	N/A
Living with the condition	

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with B-cell ALL (Philadelphia positive) in March 2014. I had an allogeneic stem cell transplant in June 2014, on my thirtieth birthday. A year after I was originally diagnosed, I had a molecular relapse, which was was kept in check by TKIs and further cells from my donor. A year after that, I had a full relapse. I was then accepted onto a CAR T-cell trial at the University of Pennsylvania, and received the treatment in June 2016. ALL comes on quickly. For me, it was a persistent cough, night sweats and a creeping tiredness that one day left me falling asleep in the GP's waiting room ready for a blood test. From the point of diagnosis, everything except the day ahead drops out of focus, and such is life for the foreseeable future. Chemotherapy was unpleasant, but an arsenal of anti-sickness drugs meant I coped relatively well. My energy levels were wiped out, resigning me to the sofa for much of the time. My heart goes out to the patients who are used to having high levels of energy and drive; the routine is repetitive, and you are going to get to know your Bargain Hunt experts particularly well. I was generally grateful to spend five nights in a row in my own bed. Chemotherapy leaves you with very low numbers of white blood cells and thus a severely impacted immunity. Infections come easily, and often. I was regularly in hospital on courses of IV antibiotics. The lack of immunity cuts you off from much of society. You are forced to avoid anywhere with a risk of contact with germs. I consider myself unbelievably lucky to have had a strong circle of family and friends to support me; without it this would be an extremely lonely illness indeed. I cannot give a true perspective of the carer; one advantage of being a patient is that you can bury yourself in cartoons, visits from friends and the Playstation. I do know however that my wife Kate gave up work for a significant stretch of time to look after me, and we leaned on our parents a lot. Our flat had to

	be kept incredibly clean to reduce infection risk, and all food had to be prepared carefully for my 'clean diet' (you would not believe how many times I have washed my hands since 2014!). She was my chef, my cleaner, my chauffeur and my crutch. I cannot begin to imagine the emotional toll it must have taken on her, but I am fortunate that she hid the burden from me in all but the most distressing moments of our journey.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The day that I received my diagnosis, my wife Kate was travelling in Myanmar. I had to break the news over a crackly phone line, akin to a call between Mission Control and the moon. It struck me how lucky I was to be in the UK and not Myanmar, as a UK citizen receiving treatment on the NHS. Nothing I experienced henceforth led me to believe any less. I also felt fortunate to be getting the illness in 2014, not 2004, because it seems like we are in an age where treatment options are advancing quickly. Some of the chemotherapies might be a bit long in the tooth, but the stem cell transplant felt like a cutting edge medical marvel; just a small bag of liquid to give me a whole new bone marrow, a whole new immune system, and a chance. The TKIs available to me post-transplant helped keep my leukaemia in check for about a year, and when I reacted badly to one, another was available. That said, I was still only given survival odds of 50:50 before my stem cell transplant. Following my full relapse in 2016, I was told the options had run out and palliative care was the next step. It is due to the extreme generosity of over 20,000 people paying for my treatment in Philadelphia that I am not talking to you from beyond the grave today, but I am all too aware that there are many, many others in this country who have not been as fortunate as me. This is evidently still a disease with poison in its talons, and thus not one to turn our back on.

8. Is there an unmet need for patients with this condition?	In a word, yes. I have done my utmost to avoid statistics and prognoses over the last 4 years, but I have always known that the outlook was relatively poor given my Philadephia-positive diagnosis. My relapse in 2016 meant that life was not just running out for me, but was coming to a screeching halt. While I prepared to see out the remaining weeks with my family, my wife would not accept defeat. We had heard about the almost mythical successes of a trial in the USA, and she was determined to get me onto it. Thanks to her indestructible belief and the generosity of all those who donated to the #Donate4Mike campaign, I was able to get onto the CAR T-cell trial at the University of Pennsylvania. As such, I stand here now over two years later. If you'd like to pinch me afterwards, come and join in. I am still having to do it to myself every day. This is evidently a technology that can offer significant hope where once there was none.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	I believe the easiest way to demonstrate this is by means of comparison between the stem cell transplant and the CAR T-cell infusion. Both started with an extremely small bag of transparent liquid, and both involved a long stay as an in-patient. I believe I was kept in for between 5 and 6 weeks after my stem cell transplant, waiting for neutrophil levels to rise to a level safe enough to leave my double-doored bubble of sanctuary. My main memory of the recovery post-transplant was one of tiredness and infections. I slept a lot, watched every minute of the 2014 World Cup and got a bit snappy at my parents as boredom kicked in a few weeks in. In Philadelphia, the length of time as an in-patient was similar, but the experience was very different. I

	reacted to the small dose of CAR T-cells within a matter of hours, and embarked on a difficult journey of high temperatures, zero sleep and two visits to intensive care. I will go into a bit more detail about this when I discuss the negative sides of the treatment, but my point is this: it was an extremely tough ride, for myself and my immediate family. However, I draw these comparisons to highlight where the marvel of this treatment really comes into its own, at least in my experience: 1. Chemotherapy, steroids and TKIs were having little effect on my leukaemia following relapse; at the start of my CAR T-cell treatment, my bone marrow contained 90% leukaemia blasts. 2. Within 28 days of the T-cell infusion, a bone marrow biopsy revealed that I had achieved deep remission. 3. Following the stem cell transplant, recovery was incredibly slow and laborious. My energy levels were extremely low, and my physiotherapist wife had to work hard to get me walking short distances. I would say that it took a year before I felt I was returning to a reasonable level of energy and fitness. On the other hand, following an extremely tough stay as an in-patient after the T-cell treatment, recovery was so fast that I was walking up mountains in the Lake District within 3 months. 4. This is probably more a case of personal fortune again, but I am currently on no medication whatsoever. I get the bus into town to work a normal job and pop to the shops on my way home, however busy it is. Last weekend I ran 10km. I have ambitions to run the Half Marathon, although if my consultant is reading this - I promise some of it will be walked…
Disadvantages of the technology	

10. What do patients or carers think are the disadvantages of the technology?	Leading up to my participation in the trial, I was warned by my various doctors that the treatment was hard. I nodded, and thought, 'Well I've had the flu, and although it won't be fun, I'll still get to watch tons of sport on the telly, so, y'know…'. They weren't lying, and to say I underestimated the experience is like saying that an elephant sitting on your lap is mildly uncomfortable. Within hours of my dose of CAR T-cells, my temperature had quickly propelled me into fever. I spent the next few days struggling through to the next dose of Paracetamol, with my wife and my mum covering me in a never-ending supply of ice packs. I've never had malaria, but that is my best reference point so far. When we thought it had peaked, the cytokine release syndrome (I prefer 'cytokine storm') went into overdrive and pushed me closer to the precipice. I spent around eight days in intensive care, with two or three visits to the MRI machine because of concerns over swelling in my brain. I was delirious and struggled to answer questions about where I was. This was possibly from total lack of sleep, the high temperatures or the excess fluid that had started gathering in my lungs. My blood pressure stayed extremely low, so this was topped up with regular bags of fluid. With the constant flow of intravenous fluids entering my body, I became extremely fluid overloaded (peaking at an extra 40kg). This left me unable to walk, and it took extensive cajoling from my family over the next few weeks to gradually get me back on my legs. My kidneys took a hit as a result, and remain something that I need to keep an eye on. I've tried to be completely honest about the full extent of how tough my experience was, but this serves only to further highlight my previous point: once these magical super T-cells had done their work, wiping away leukaemia from a marrow previously teeming with blasts, my recovery from this point was remarkable. Again, I repeat, I was walking up mountains in the Lake District within 3 months. Mentally, it took some time to come to terms with what happened to me, but physically the turnaround felt almost miraculous.
Patient population	

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

14. What do patients and carers think about using the new technology considering the risk of severe adverse events occurring?	
15. What to patients and carers think about the need to remain in close proximity to the treatment centre for 1 month following treatment with the new technology?	
16. What do patients and carers think of the extended hospitalisation required during treatment with the new technology?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- ALL is a fast-acting disease, with a treatment that takes its toll on the body, leaves you unable to participate in most normal activities and can severely limit social contact.
- Although available treatments can cure, success rates are not high, and a relapse following stem cell transplant leaves you with few to no options moving forward.
- In comparison to the stem cell transplant, CAR T-cell treatment was intensive and emotionally draining as an in-patient, but following release from hospital the speed of recovery was remarkable.
- CAR T-cell treatment offers hope to those whose transplants have not worked, or indeed to those whose leukaemias may have resisted initial courses of chemotherapy. I can only imagine where this technology may take us in future, but it feels like we are at the start of something special.
-

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

1.

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your organisation's 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 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 10 pages.

About you	
1. Your name	**Claire Foreman**

2. Name of organisation	**NHS England**
3. Job title or position	**National Programme of Care Senior Manager – Blood and Infection, Specialised Commissioning, NHS England**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England** NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**

Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE have published several technology appraisals relating to the treatment of leukaemias of various types. NHS England has published a service specification in relation to the provision of chemotherapy in cancers and haematopoiec stem cell transplants which follow BSBMT guidelines. Relevant policies and specifications can be viewed here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for the current diagnosis of and available treatments for leukaemia is well defined. A national algorithm is in draft which will define the treatment pathway for chemotherapy in leukaemias. The proposed intervention, a type of chimeric antigen receptor t-cell (CAR-T), and its place in therapy is yet to be well defined because it is a new treatment and has a novel mode of administration. This includes the logistics of providing the intervention and the services which will ultimately provide treatment assuming the product receives a positive NICE guidance. Cancer services in England are split into paediatric, Teenage and Young Adult (TYA) and adult services. This configuration has developed to ensure that TYA cancer patients no longer fall between the gaps between paediatric and adult services and that the specific needs of this age group are considered. This will be an important principle to address when identifying providers able to deliver the treatment.
8. What impact would the technology have on the current pathway of care?	As an innovation in personalised medicine, this technology has the potential to revolutionise current treatment strategies for patients and offer the potential for cure. The extent of the impact on outcomes and the time taken to achieve its potential is as yet unknown. Although the allogeneic stem cell transplant pathway will provide some guidance, the technology will require new pathways for the preparation of patients, manufacture of the medicine, delivery of the medicine and long-term monitoring of the patient. Detailed scheduling of the patient care pathway will be required. NHS England understands there will be significant technical and other service support that is required in order to provide CAR-T therapy in a safe

	environment. The initial uptake and impact of the treatment is likely to be low until appropriate resources and infrastructure are in place to deliver CAR-T. Severe, life threatening, adverse events are not uncommon and this will have an impact on the pathway, requiring an increase in intensive care support compared to the current pathway. The paramount focus on safety is likely to necessitate 'ramp-up' access over a period of time to allow for manufacturing and care delivery capacity to develop. This will include manufacturer to NHS provider contracting, ongoing training, ongoing accreditation, assured access to ITU capacity etc.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Currently, CAR-T is available through research trials only. The patient group is those with haematological cancers, although the research pipeline is such that the indications for use are expected to expand over time If the technology receives a positive NICE guidance, it is likely to be used in accordance with its licence in those patients who are eligible for treatment and who want to undertake the treatment. However, the infrastructure to support the implementation of a safe treatment environment will need to be in place before access can be allowed. NHS England is aware that lead-in time from the company's perspective may be as long as 6 months to complete the quality assurance for manufacture and to complete training. The eligible population is relatively small (circa 30-40 per year). This means the right balance of geographical spread and concentration of expertise will be challenging and required from the start.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not currently available within the NHS except as part of ongoing trials. The technology is significantly different to current care and will require a new service specification against which dedicated providers will be designated and established. The specification for this and another CAR-T product is currently in development. NHS England believes the manufacturer will seek phased implementation.

	The importance of clinical expertise cannot be underestimated. In term of allogeneic stem cell transplantation, providers are expected to undertake c10 transplants a year. Given the small eligible population, getting the right balance of access and commissioned providers will need to remain under review and may be subject to change over time. The requirements for treatments before and after CAR-T (e.g. HSCT) need to be clarified.
• How does healthcare resource use differ between the technology and current care?	Although some of the requirements for CAR T are similar to those of allogeneic stem cell transplantation, this new treatment will require significant infrastructure changes to support access including access to (paediatric or adult) intensive care (ITU) beds, specialist pharmacy resource, access to neurosurgical support and other supportive drugs such as tocilizumab to treat potential side effects of treatment such as cytokine release syndrome and tumour lysis syndrome. This is in contrast to provision of chemotherapy which does not require this level of infrastructure support. Although the licence is awaited to confirm the particulars, it is expected that patients will either need to be admitted for the administration of the treatment and for a period thereafter (possibly 4 weeks) or that ambulatory care after about 2 weeks post infusion is a possibility. The patient needs to remain within a certain distance of the provider for 4 weeks with access to immediate medical attention. The distance from the provider is subject to debate. As this is a one-off treatment requiring new and considerable infrastructure / supportive care compared to chemotherapy which is well established and given over a number of cycles, determining the actual cost of treatment will require detailed work and is expected to be considerable. The payment mechanism for the treatment will therefore need reviewing if a positive NICE guidance is published. Assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult as there are a range of local currencies and prices for allogeneic transplant in England. NHS England considers the need to start with the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy.
• In what clinical setting should the technology be used? (For example,	Tertiary / cancer centres that provide allogeneic stem cell transplants and have ready access to specialist pharmacy services, ITU and neurosurgery. The service will need to be JACIE accredited for Immune Effector Cell Therapy and meet the requirements of the pharmaceutical company with respect to handling the product in accordance with the medicines regulations. It is unclear the exact requirements of the

primary or secondary care, specialist clinics.)	supplier with regard to quality assurance and contracting with provider sites, as there is a complex process and supply chain associated with the therapy. NHS England is drafting a new service specification to outline the requirements which will be specific to each CAR-T therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As above. Staff on site will need to be trained on the handling and provision of the product and we understand this will be provided by the company as part regulatory requirements. Specialist equipment may also be required. This will include training for pharmacy staff who will be required to handle and store the final product before administration to the patient, in accordance with the regulation of medicines. Since the final product will be delivered frozen in vapour phase nitrogen and therefore special equipment may be required for storage while the patient undergoes conditioning. EEG and emergency neurology to monitor adverse events may also be required. Ways of managing the increased demand for ITU will be required.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	CAR-T is a one-off treatment. Starting criteria will depend on any marketing authorisation (MA) received and any conditions put upon access by NICE Guidance and NHS England. Clinically, it is proposed that a National MDT structure may be needed to be put in place while capacity is being established to ensure appropriate patient selection for new CAR T treatments. NHS England will put this in place. Patients will need to undergo a conditioning regimen and this does pose additional complexities with timing of treatment and access to the final product which is shipped in from US and Europe. The supplier will, as part of their risk management plan, need to ensure contracts are in place with NHS provider sites. Test runs are performed before live product is used to ensure the supply chain works effectively. Re scheduling of patient selection, manufacture and treatment, we understand there will also need to be a window of +20 days between treatment of patient 1 and 2 for the purposes of providing a buffer to manage issues and risks.

11. What is the outcome of any evaluations or audits of the use of the technology?	No audits have been undertaken. Trial data is available based on 8 month follow up.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Due to the novelty of the treatment and the logistics involved, all key stakeholders have indicated the need for a phased implementation if approved. This is likely to mean that geographical access at the start will be worse than current access to chemotherapy / HSCT. It is expected that this would be redressed over time as experience and capacity improves and more accredited providers can be supported to offer the treatment. However, it is not anticipated that all allogeneic transplant providers would be commissioned to deliver this treatment.
12b. Consider whether these issues are different from issues with current care and why.	These issues are different to the current pathway due to the novelty of the treatment, the complexity / toxicity profile, the interdependence on other services, capacity in the supply chain and the experience of the system in delivering the treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission for NICE appraisal of tisagenlecleucel for the treatment of patients aged up to 25 years with relapsed/refractory acute lymphoblastic leukaemia (ALL)

Redacted version

EMA marketing authorisation and place in treatment pathway

1. Tisagenlecleucel (T-L) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients aged up to 25 years with B cell ALL who are 1) refractory to treatment or 2) have relapsed post stem cell transplant (SCT) or 3) in 2nd or later relapse.

2. Novartis split the likely patient composition according to these 3 clinical scenarios as follows: [redacted] have refractory disease, [redacted] are post-SCT and [redacted] are in 2nd or later relapse. NHS England agrees that only a small percentage of eligible patients will have refractory disease.

3. For patients to be refractory, this has to mean that they have disease that has not responded to induction chemotherapy whether it is given 1st or 2nd line. The practical consequence is that patients who respond to 1st line induction chemotherapy but relapse on either 1st line consolidation or maintenance therapy do not qualify for T-L on the grounds of not having refractory disease. The numbers of patients with disease refractory to 1st line therapy are small and were also small in the T-L trials. NHS England observes that the current standard treatment for disease refractory to 1st line induction in those aged less than 18 years is mainly using the NOPHO protocol. This was not recognised in the company's submission. For those aged over 18 years (a much smaller group), the current treatment is blinatumomab or combination chemotherapy and more likely to be blinatumomab.

4. For patients who respond to 1st line induction and then relapse, the aim of treatment is attain a second remission and then consolidate this with an allogeneic SCT. For patients who relapse post-SCT, the company has stated that the standard comparators are either combination cytotoxic chemotherapy FLA(G)-IDA or the CD19-targeted monoclonal antibody blinatumomab. The company states that FLA(G)-IDA and blinatumomab are also the comparators for patients in 2nd or further relapse.

5. Blinatumomab is a specific T-cell engager antibody which binds specifically to CD19 expressed on the surface of cells of B-lineage and also to CD3 expressed on the surface of T cells. It thus activates T cells by connecting the CD3 on the T cell with CD19 on benign and malignant B cells. Blinatumomab is recommended by NICE as a treatment option in adults with relapsed/refractory Philadelphia chromosome negative ALL. Blinatumomab access has been extended to the non-adult ALL population by NHS England. The administration of blinatumomab is inconvenient and demanding for patients and clinical staff. Of note too is that approximately 22% of patients who relapse post blinatumomab do so with ALL which no longer expresses CD19.

6. T-L CAR T cell therapy also targets CD19 and as a consequence there is therefore a concern that patients previously treated with blinatumomab and who then relapse may have clones of B cells which do not express CD19. In such circumstances, treatment with T-L would therefore not be expected to have any significant chance of curing the patient. The 3 T-L trials excluded patients previously treated with blinatumomab and thus there is no evidence of the efficacy of T-L in patients previously treated with blinatumomab. As a consequence of the biological plausibility of prior blinatumomab reducing the benefits of CAR T cell treatment directed at CD19 plus the exclusion of patients with prior blinatumomab exposure in the T-L trials, there will be wariness by haematologists in the use of blinatumomab if CAR T cell therapy with T-L is a potential salvage therapy later in the treatment pathway.

7. Although combination chemotherapy and blinatumomab were commissioned options for relapsed/refractory ALL at the times of the NICE scope and the Novartis and ERG submissions, inotuzumab ozogamicin is now NICE-recommended in adults with relapsed/refractory ALL and funding has been extended to children by NHS England. Inotuzumab is directed against CD22 and thus does not carry any biological plausibility in potentially reducing the benefits of subsequent T-L therapy. In addition, it is a much more convenient drug to receive and deliver than blinatumomab. Hence it is likely to rapidly displace much use of blinatumomab and especially so in the relapsed/refractory ALL population in which CAR T cell therapy with T-L could be an option later in the treatment pathway. The administration costs of inotuzumab are much less than for blinatumomab and it is likely that drug procurement costs (based on the list prices of the two drugs) will also result in inotuzumab costing less than blinatumomab. As inotuzumab results in higher rates of CR and SCT than combination chemotherapy at 1st relapse, it is likely to become the treatment of choice at this place in the treatment pathway.

8. NHS England notes that that at the time of the NICE scope, NICE stated that the comparators for T-L should be ‘established clinical management without T-L’. NICE did list the inotuzumab appraisal in the March 2018 scope as an appraisal in development. Although NHS England recognises that inotuzumab is not yet in August 2018 a part of ‘established clinical management’, it will become so in the very near future given its obvious practical advantages.

9. NHS England concludes that the comparator for 1st line refractory patients should be mainly the NOPHO protocol as this is used in children and teenagers and blinatumomab in the young adult population. Currently, there is also some blinatumomab use in the younger populations rather than the NOPHO protocol but such use of blinatumomab (whatever the age) is likely to diminish in favour of inotuzumab.

10. For the much larger T-L eligible populations of relapsed post-SCT and in 2nd or further relapse that have not had SCT, the comparator options are currently the same treatments in these 2 places in the treatment pathway and depend on what has been used previously – if chemotherapy is used at 1st relapse, then the comparator at 2nd relapse would be blinatumomab (though shortly to

be inotuzumab); if blinatumomab is used at 1st relapse (and shortly to be replaced by inotuzumab), then the comparator for 2nd relapse would be chemotherapy, the most commonly used regimen being FLA(G)-IDA or the ALLR3 protocol (which is similar to FLA-IDA although given for longer) or the combination of clofrabine, cyclophosphamide and etoposide. As has been stated above, treatment for 1st line relapse is likely to become inotuzumab in the near future and hence these same 2 options of blinatumomab and FLA(G)-IDA apply as comparators for T-L. There is little data on the use of blinatumomab after previous inotuzumab although there is no biologically plausible reason as to why blinatumomab should not be active. However this lack of evidence may affect the choice of treatment.

11. Estimation of SCT rates in England is also complicated by the fact that NHS England only commissions a 2nd SCT in ALL if the 1st SCT resulted in a remission of 1 year or more.

12. In summary, it is likely that at 1st relapse blinatumomab is currently offered but this will be replaced by inotuzumab in the imminent future. Thus the one definite comparator in the right place in the treatment pathway for the appraisal of T-L is combination chemotherapy as the great majority of the patients in the marketing authorisation are post-SCT or post 2 lines of treatment. Once inotuzumab is in established practice, it is likely that in patients failing 2 lines of treatment (1st line chemotherapy and then 2nd line inotuzumab with or without SCT), 3rd line treatment would be chemotherapy or blinatumomab. The paucity of data as regards the activity of blinatumomab after inotuzumab may affect the choice of treatment in favour of chemotherapy.

13. The Ph pos ALL population is very small in young patients with ALL and there is no biologically plausible reason as to why such patients would not be treated with T-L CAR T cell therapy. NHS England notes that such patients were included in the T-L trials.

Potential patient numbers for whom tisagenlecleucel would be indicated

14. In total, NHS England estimates that there will be about 25-30 patients with ALL in the age range specified in the T-L marketing authorisation who will be appropriate to receive treatment if NICE recommends T-L. There are active CAR T cell clinical trials in this ALL indication which may offset the number of patients that would require NHS funding.

Tisagenlecleucel trial outcomes

15. NHS England notes that [redacted] patients were screened for these 3 T-L trials, [redacted] patients were formally enrolled in them and [redacted] were infused with T-L. Thus about [redacted] and [redacted] of the screened and enrolled patients actually received the intended treatment, respectively. NHS England would only wish to pay for T-L in those patients who actually receive T-L treatment.

16. NHS England considers that the highly selected patients in the 3 phase 2 T-L trial populations are generalizable to the also highly selected population of patients in the NHS which would be treated with T-L. However there is one big difference and that will relate to previous treatment. Currently many potential T-L candidates will have had prior treatment with blinatumomab in the NHS but such prior therapy was excluded from the T-L trials. Thus prior treatment with blinatumomab is likely to change as inotuzumab is increasingly used (see above).

17. The current median durations of follow up in the 3 T-L trials were between [redacted] and [redacted] months and the last data cuts varied between [redacted] and [redacted]. The efficacy results for T-L in patients with relapsed/refractory ALL and within the marketing authorisation are thus immature and NHS England notes that some of the data analysis is not particularly recent. The latter is disappointing given the importance of reducing uncertainty in this appraisal.

18. NHS England notes that event free survival (EFS) is plateau**ing** in the pooled EFS analyses but events have still occurred at [redacted] months. EFS rates at 1 year were [redacted], at 2 years were xxx and at 3 years were [redacted]. NHS England notes that there are very few patients at risk after [redacted]months and so regards these EFS results as very encouraging but not mature and thus uncertain. The plateauing of EFS is based on very few patients at risk.

19. Overall survival (OS) in the pooled T-L studies is also plateau**ing** but NHS England notes that deaths have occurred beyond [redacted] years. The 1 year OS figure is [redacted], the 2 year figure is [redacted] and the 3 year OS rate is [redacted]. There are [redacted] patients at risk after [redacted] years. NHS thus notes that OS rates are [redacted] and that there are few patients at risk after [redacted] months. The OS data has to be regarded as being very promising but still uncertain. The plateauing of OS is based on very few patients at risk.

20. The fact that rates of EFS and OS have not yet plateaued in a young population with an aggressive malignancy is evidence of the immaturity of the T-L data, this being in contrast to the established long term outcomes after SCT in ALL.

21. NHS England notes that these T-L EFS and OS rates are in the infused patients, not the enrolled patients. This is correct in terms of assessing the outcomes of T-L therapy but does mean that the costs of the [redacted] of patients who are leucapheresed but not T-L infused need to be added to the cost of T-L treatment in the economic analysis (until the time of the decision not to treat with T-L).

22. NHS England notes that [redacted] of T-L patients had subsequent allogeneic SCTs in the pooled 3 T-L studies. The OS rates (albeit based on small numbers) appear better in those patients who had SCTs. The reasons for this use of SCT are not entirely clear but one important reason could be the progressive loss of CAR T cells in these patients as such a loss would be regarded as a prelude to disease relapse. NHS England expects therefore for there to be a

definite rate of SCT to be observed in T-L treated patients if T-L is recommended by NICE in this indication and estimates this to be in about 15% of patients.

23. NHS England also notes that [redacted] of the T-L phase 2 study B2101J received further infusions of T-L. The contribution of this to the OS rate is not known.

Indirect comparisons of tisagenlecleucel with chemotherapy and blinatumomab

24. NHS England notes that Novartis used clofarabine monotherapy data as the proxy for combination chemotherapy with FLA-IDA. The clofarabine data was use of clofarabine monotherapy, not combination treatment (single-agent cytotoxic chemotherapy is very rarely used in acute leukaemia). The clofarabine monotherapy data was old, the first patient being treated in 2002 and the data cut off was in September 2004. Supportive care has changed much since 2002-2004 with significantly improved outcomes, including in the access to and the speed of access to SCT donors. This therefore means that the outcomes in the clofarabine monotherapy dataset are likely to be inferior to those of the combination FLA-IDA given in in a more contemporaneous time.

25. The indirect comparison of the pooled T-L studies with old clofarabine monotherapy data used as a proxy for FLA-IDA is inappropriate as there is more contemporaneous data for FLA-IDA (according to the ERG) with greater numbers of patients and longer median duration of follow-up. The heterogeneity of the data in any indirect comparisons of T-L with chemotherapy and also with blinatumomab is noteworthy.

Utilities in the economic model

26. NHS England notes the utility decrement of 0.57 which Novartis has applied to the first year following an allogeneic SCT. Whilst the morbidity of such SCTs is very substantial, the decrement of 0.57 for a duration of 1 year is inconsistent with the population being young (and who recover relatively quickly) and as a consequence patients can be frequently back at school after 6 months. The decrement duration thus seems excessive.

Tisagenlecleucel toxicity

27. NHS England notes that treatment with T-L is associated with many side-effects, some of them being life threatening and particularly so in the first month of treatment. It observes that serious toxicity may diminish as experience with CAR T cell therapy increases but nevertheless recognises that it has to wrap all the appropriate 24 hour expertise around each patient in order to maximise safety and optimise outcomes for patients and the NHS. In the 3 T-L trials, about 90% of patients experienced a grade ≥3 adverse event,

about 80% a grade ≥3 serious adverse event and [redacted] of patients died in the first 30 days.

28. The two most dangerous side-effects of T-L are of cytokine release syndrome (CRS), encephalopathy and febrile neutropenia. Feedback to NHS England from the clinical trial centres in England which are currently involved in CAR T cell therapy consistently report how diverse the manifestations of toxicities can be and how alert patients and staff must be to apparently minor symptoms which can then escalate quickly if not heeded and acted upon.

29. 83% of patients recorded some degree of CRS but it is in 43% that grade 3 or worse CRS was seen. CRS occurs soon after treatment with T-L. Mild/moderate CRS requires considerable observation and supportive care but more severe CRS needs full intensive care plus the administration of tocilizumab and steroids. NHS England notes that the admission rate to intensive care units was about 50% and that the median stay was about 7 days. NHS England observes that 46% of patients in the ELIANA T-L study required treatment with tocilizumab. The need for training for all staff from the haematological ward to the intensive care unit is very great as the manifestations of CRS are so diverse and unexpected.

30. Another significant side-effect is hypogammaglobulinaemia. B-cell ablation is a pharmacodynamic measure of successful treatment with CAR-T cell products directed against leukaemia of B-cell origin. Loss of circulating B-cells and consequent drastic falls in serum immunoglobulin (Ig) levels, also known as agammaglobulinaemia, is a predictable on-target off-tumour effect of T-L.

31. The pivotal study on T-L in children and young adults with refractory acute lymphoblastic leukaemia (Maude et al. New Eng J Med 2018;378:439-48) showed that all patients responding to CAR-T cells developed B-cell aplasia and *most* of these 75 patients (exact number not specified) received IVIg. The probability of B cell recovery was [redacted] at 12 months but NHS England notes that this figure did not change at [redacted] months (albeit based on small numbers).

32. From the point of view of a clinician looking after these highly immunosuppressed patients who all undergo conditioning chemotherapy prior to CAR-T cell treatment, there is bound to be considerable anxiety associated with merely observing a patient with no circulating B cells and Ig, as opposed to intervening with prophylactic Ig. Until there is solid longitudinal data on the infection risks associated with CAR-T cell associated agammaglobulinaemia, there is bound to be great and clinically justifiable pressure to use prophylactic Ig.

33. Whilst it is not expected that every patient who receives a B-cell directed CAR-T cell treatment will require IVIg, it is predicted that the majority of responders to CAR-T cells will do so. For the purposes of costing IVIg requirements, long term follow up data on the proportion of patients who developed B-cell aplasia and low Igs as a consequence of CAR-T cell therapy is required. Until that is known, a pragmatic estimate of that up to 50% of

responders will require IVIg (until B cell aplasia recovers) for a period of 12-24 months would not be unreasonable.

34. As regards route of delivery, both intravenous Ig (IVIg) and subcutaneous Ig (SCIg) would be equally efficacious. Given that CAR-T cell therapy will be limited to major haematology centres, it is expected that the majority of those patients requiring Ig will be able to undergo training for home administration of SCIg.

35. IVIg and SCIg are costly interventions and thus could have a significant impact on the mean cost of the supportive care that has to be wrapped around each patient who responds to T-L.

Economic modelling

36. NHS England notes that in its economic model Novartis assumes that T-L results in a OS rate of 45% at 5 years. In the pooled analysis, the OS rate is 55% at 3 years, events are still occurring (EFS is 41% and events are still occurring at 3 years) and a few OS events can make a large difference to the 5 year OS rate. NHS England regards the Novartis OS rate at 5 years as being optimistic and considers that the lower rates of 34-36% preferred by the ERG are much more realistic.

37. The Novartis economic model assumes that the overall survival for cured patients is based on the mortality decline of the general population. NHS England regards this as being incorrect as these patients have been heavily pre-treated with chemotherapy which is known to add a continued survival disadvantage in the long term.

38. NHS England observes that the Novartis economic model assumes a long term OS rate of 11-12% with blinatumomab. The registration trial of blinatumomab cannot be directly compared with the T-L trials owing to some degree of heterogeneity but blinatumomab achieved a 34% CR rate, a 24% SCT rate and thus an expected long term cure rate of about 13%. Expert opinion to NHS England indicates that there were extended times to SCT in the TOWER blinatumomab trial and thus the SCT rate in practice is expected to be higher than 24% and thus the long term OS rate is likely to be about 15-18%. The difficulty here is that blinatumomoab is likely to be relegated to treatment at 2nd relapse after previous inotuzumab and thus the rates of CR, SCT and long term OS are not known when confined to this stage in the treatment pathway whether there is or not any cross resistance between the 2 monoclonal antibodies.

39. NHS England observes that the Novartis economic model assumes a long term OS rate of 3% following FLA(G)-IDA and that the ERG's figure is 14%. Expert opinion to NHS England indicates that the CR rate with combination chemotherapy is likely to be about 25-30%, the SCT rate is 15-20% and the long term OS rate is about 10%.

40. NHS England notes that in the Novartis model, the mean life years gained (LYG) with FLA-IDA is xxx years and with blinatumomab is [redacted] years. The median values would be much less. NHS England also notes that the LYG with T-L is [redacted], a figure that contrasts sharply with the median duration of follow-up measured in months in the T-L trials, and thus demonstrates very clearly the degree of modelling that is being used in these health economic estimations of T-L clinical and cost effectiveness.

41. NHS England plans to ensure that patients remain within a 2 hour travel time for the first 4 weeks after CAR T cell treatment. Some patients may be able to stay with relatives/friends but many will require either hostel or hotel accommodation. These costs of patients having to remain close to treating centres need to be included in the economic analysis.

42. NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. A sensitivity analysis is recommended which uses the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for T-L as ITU stay is not counted in the allogeneic SCT tariff) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy.

NHS England delivering CAR T cell therapy in practice.

43. All CAR T cell centres with be JACIE-accredited providers of allogeneic haemopoietic stem cell transplantation with onsite level 3 intensive care units with documented, sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in critical care, renal, respiratory, cardiovascular and neurological medicine. Such support must be co-located or on a directly contiguous site to both the ITU and CAR T cell treatment units. The ITU must have the availability of immediate and 24 hour electroencephalography monitoring as well as the expertise necessary for its interpretation.

44. Patients will often be inpatients for 3-7 days during their conditioning chemotherapy prior to CAR T cell infusion. They will be inpatients for a minimum of 7 days after CAR T cell infusion during which they will have twice daily assessments of cytokine release syndrome and 3 times daily testing for neurotoxicity. Patients will have to remain within a 2 hour travelling time of the CAR T cell centre for 4 weeks after infusion of T-L. CAR T cell centres will have to offer rapid admission pathways of care which offer immediate access to assessment by experienced and trained staff in managing the diverse complications of CAR T cell therapy. The provision of ambulatory care pathways in accordance with NICE Guideline (NG47) Haematological Cancers: Improving Outcomes (https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#ambulat

ory-care) will enable centres administering CAR T cells to satisfy these objectives safely whilst accommodating patient experience.

45. CAR T cell centres will have cell therapy laboratory and pharmacy expertise in the handling, storage and thawing of advanced therapy medicinal products. In addition, centres will have considerable expertise in leucapheresis.

Innovation

46. NHS England regards tisagenlecleucel as highly innovative in terms of its mode of action: genetic engineering to T cells to recruit an immune response which results in a 'living' treatment against ALL. But however clever or neat a technology may be, it is what a treatment does to meaningful outcomes for patients which results in NHS England concluding whether a new treatment is a game changer or not. CAR T cell therapy fulfils this definition of a potential game changer if it is confirmed that there are very few or no few relapses in the period beyond 36 months after treatment and if there is no substantial long term toxicity which impacts on survival.

Cancer Drugs Fund

47. Depending on the NICE committee's conclusions as to clinical and cost effectiveness, NHS England regards T-L as a good candidate for the Cancer Drugs Fund as the EFS and OS results are still not mature. Relapses are still being observed after 24 months and few patients are at risk beyond 24 months. An extra 12 months of follow-up and up to date analyses of the T-L phase 2 trials would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very costly technology.

NHS England commissioning treatment criteria

48. NHS England would wish to set treatment criteria for T-L therapy which reflects the known marketing authorisation, the relevant treatment pathways in England, the evidence base submitted to NICE and considerations to be made by the NICE technology appraisal committee. These provisional criteria are set out below.

Tisagenlecleucel as treatment for relapsed/refractory acute lymphoblastic leukaemia in patients who are refractory to induction chemotherapy or who relapse after stem cell transplantation or who are in 2nd or further relapse

1. I confirm that this application is made by and that treatment with tisagenlecleucel will be initiated by a consultant haematologist specifically trained and accredited in the use of systemic anti-cancer therapy with day to day expertise in the use of allogeneic bone marrow transplantation **and** who is a member of both the national acute lymphoblastic leukaemia multidisciplinary team and the Trust's CAR T cell multidisciplinary team

2. I confirm the patient has a confirmed diagnosis of B lineage acute lymphoblastic leukaemia that is still CD19 positive at the time of consideration of tisagenlecleucel
3. I confirm that the patient has either refractory disease to induction chemotherapy OR has relapsed after a allogeneic stem cell transplantation OR is in 2nd or further relapse (tick boxes as to which)
4. I confirm that the patient is of Karnofsky/Lansky performance status 50 or more
5. I confirm that the patient either has not received previous blinatumomab or has been treated with previous blinatumomab (tickboxes as to which)
6. I confirm that the patient does not have any significant comorbidity which contraindicates CAR T cell therapy with tisagenlecleucel
7. I confirm that the patient has had no previous therapy with any genetically modified autologous T cell immunotherapy
8. I confirm that approval for the use of tisagenlecleucel has been formally given by the national acute lymphoblastic leukaemia multidisciplinary team meeting
9. I confirm that following national approval for use of tisagenlecleucel there has been local CAR T cell multidisciplinary team agreement that this patient has the necessary fitness for treatment and fulfils all treatment criteria listed here
10. I confirm that tisagenlecleucel will be otherwise used as set out in its Summary of Product Characteristics

Prof Peter Clark
NHS England Chemotherapy Clinical Reference Group chair and clinical lead for the Cancer Drugs Fund

August 2018

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report

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

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Date completed Date completed (27/07/2018)

Source of funding

This report was commissioned by the NIHR HTA Programme as project number ID1167

Declared competing interests of the authors

None.

Acknowledgements

We would like to thank Dr Beki James, Consultant Paediatric Haematologist at Leeds Teaching Hospitals NHS Trust, for her expert clinical advice throughout the project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Walton M, Sharif S, Hodgson R, Claxton L, Wright K, Simmonds M. Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2018.

Contributions of authors

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

Note on the text

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

Copyright statement

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List of abbreviations

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

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

1 Summary

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

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

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

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

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

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

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

1.2 Summary of clinical effectiveness evidence submitted by the company

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

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

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

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

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

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

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

The systematic review presented in the CS used adequate methods to identify the relevant studies, with no relevant trials likely to have been missed.

The ERG noted some limitations regarding the representativeness of the patients recruited to the trials. All three trials restricted eligibility to patients with a life expectancy of 12 weeks or more. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. In addition, B2101J had a multiple infusion dosing regimen for tisagenlecleucel-T. This may have contributed to improved drug persistence and therefore biased long-term outcomes in B2101J.

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

between enrolment and infusion of tisagenlecleucel-T in all three trials was substantially longer than the 3 to 4 weeks estimated in the CS. This has considerable implication for eligible patients due to the pace of disease progression and their short-estimated life expectancy. In addition, the proportion of patients who received an allo-SCT after infusion in all three trials is concerning considering the curative intent of tisagenlecleucel-T.

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

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

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

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

1.4 Summary of cost effectiveness submitted evidence by the company

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The ERG also highlights the uncertainty regarding the current treatment of ALL patients with 2+ relapses in the NHS. NICE guidance is already in place for the ~8.3% of patients aged >18 years, who would typically receive blinatumomab as a first-line salvage therapy. This means this population would not be eligible for blinatumomab again after a second relapse, as considered in this appraisal. Clinical advice to the ERG and company suggests this is also increasingly becoming the case in paediatric patients, the implication being that FLA-IDA may be the most relevant comparator for patients with two or more relapses. The ERG also considers the impact of blinatumomab use earlier in the treatment pathway may raise the issue of eligibility for tisagenlecleucel-T after 2+ relapses. Patients who had previously used an anti-CD19 therapy such as blinatumomab were excluded from all three tisagenlecleucel-T trials, due to the hypothetical impact upon treatment efficacy and the chance of CD19-negative relapse, which was observed in 22% of tested relapses in the paediatric blinatumomab trial. This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy.

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

1.6.1 Strengths

Clinical effectiveness

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

Cost effectiveness

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

1.6.2 Weaknesses

Clinical effectiveness

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

Cost effectiveness

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

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

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

2) *OS data is immature for tisagenlecleucel*

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

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

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

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

4) *Uncertainty surrounding broader infrastructure and training requirements*

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

5) *Uncertainties surrounding adverse events*

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

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

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

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

- The source of clinical data used to estimate the survival of patients on salvage chemotherapy
- The duration of B-cell aplasia duration and costs of IVIG,
- Post-SCT quality of life and anticipated SCT uptake in practice,
- Number of lines of blinatumomab treatment modelled,
- The health state utilities used in the model.

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

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

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

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

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

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

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

2 Background

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

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

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

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

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

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

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

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

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

2.2 Critique of company's overview of current service provision

2.2.1 Treatment pathway

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

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

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

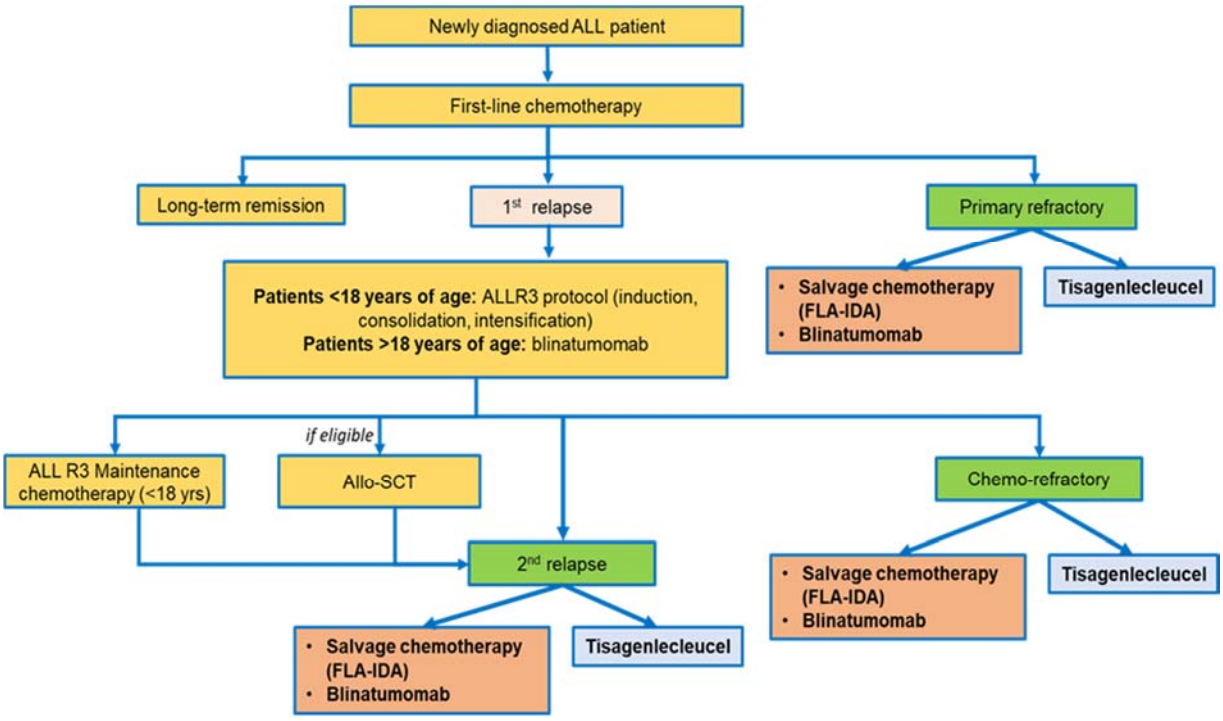
First line treatment for both paediatric and TYA patients consists of multi-drug chemotherapy, which typically includes a combination of cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine [28]. Figure 1 Clinical pathway of care for patients with B-cell ALL and potential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

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

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

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

Figure 1 Clinical pathway of care for patients with B-cell ALL and potential positioning of tisagenlecleucel-T (Figure 6 of the CS)



Abbreviations: ALL: acute lymphoblastic leukaemia; allo-SCT: stem cell transplantation; FLA-IDA: fludarabine, cytarabine and idarubicin.

3 Critique of company's definition of decision problem

3.1 Population

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

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

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

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

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

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

3.2 Intervention

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

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

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

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

3.3 Comparators

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

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

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

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

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

3.4 Outcomes

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

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

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

3.5 Other relevant factors

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

4 Clinical Effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

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

Reporting

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

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

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

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

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

Strategy

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

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

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

4.1.2 Inclusion criteria

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

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

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

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

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

4.1.3 Critique of data extraction

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

4.1.4 Quality assessment

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

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

4.1.5 Evidence synthesis

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

4.2 Critique of trials of tisagenlecleucel-T

4.2.1 Tisagenlecleucel-T studies

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

The ERG noted some limitations and concerns about the representativeness of the patients recruited to the trials. All three trials restricted eligibility to patients with a life expectancy of 12 weeks or more. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. The ERG is unsure whether primary refractory patients would be treated with tisagenlecleucel-T in practice, given that clinical advice to the ERG highlighted that current treatment is effective in these patients [30]. Therefore, the populations in all three studies may be broader and healthier than expected in NHS practice.

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

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

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

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

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

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

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

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

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

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

4.2.1.1 Key properties of ELIANA

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

4.2.1.2 Key properties of ENSIGN

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

4.2.1.3 Key properties of B2101J

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

4.2.2 Results of the Tisagenlecleucel-T trials

4.2.2.1 ELIANA

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

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

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

Figure 2 Kaplan-Meier curve for EFS from enrolment in ELIANA

Figure 3 Kaplan-Meier curve for OS from enrolment in ELIANA

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

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

Figure 4 Kaplan-Meier curve for OS by whether received post-infusion allo-SCT in ELIANA

Figure 5 Kaplan-Meier curve for EFS (without censoring for allo-SCT) by whether received post-infusion allo-SCT in ELIANA

The CS included pre-specified ORR subgroup analyses for subgroups with at least five patients (presented in section B.2.7). However, these were not available for the latest data cut off (31st Dec 2017) but only for the data cut-off 25th April 2017. The CS concluded that the ORR was consistently ≥ 55% across all subgroups confirming the robustness of the primary analysis. However, these analyses were only done in the full analysis set not the full ITT population.

Patient reported outcomes

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

Figure 6 Summary of PedsQL and EQVAS scores in ELIANA

4.2.2.2 ENSIGN

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

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

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

Figure 7 Kaplan-Meier curve for EFS from enrolment for ENSIGN

Figure 8 Kaplan-Meier curve for OS from enrolment for ENSIGN

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

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

Figure 9 Kaplan-Meier curve for OS whether received post-infusion allo-SCT in ENSIGN

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

4.2.2.3 B2010J

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

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

Figure 11 Kaplan-Meier curve for EFS from enrolment in B2101J

Figure 12 Kaplan-Meier curve for OS from enrolment in B2101J

Figure 13 Kaplan-Meier curve of OS from B2101J with censoring for allo-SCT

4.2.3 Meta-analysis

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

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

The pooled data included [redacted] patients, for which EFS and OS were assessed (**Figure 14** and

Figure 15, respectively). The CS reported the probability of being event-free was [redacted]% at one year, [redacted]% at two years and [redacted]% at 3 years. Median EFS was [redacted] months and [redacted]% of patients reported an EFS event. Median OS was [redacted] months and [redacted]% of patients had died following tisagenlecleucel-T infusion. The probability of survival at one year was [redacted]% and [redacted]% at 2 years However, the median OS should be interpreted with caution, as there are very small numbers of patients at risk beyond 38 months.

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

Figure 14 Kaplan-Meier curve for EFS in ELIANA, ENSIGN, B2110J and the pooled analysis

a

Figure 15 Kaplan-Meier curve of OS in ELIANA, ENSIGN, B2101J and the pooled analysis

4.2.4 Adverse events of tisagenlecleucel-T

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

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

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

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

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

4.3.1 Comparator treatment studies

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

4.3.1.1 Blinatumomab

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

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

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

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

4.3.1.2 Clofarabine and salvage chemotherapy (FLA-IDA)

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

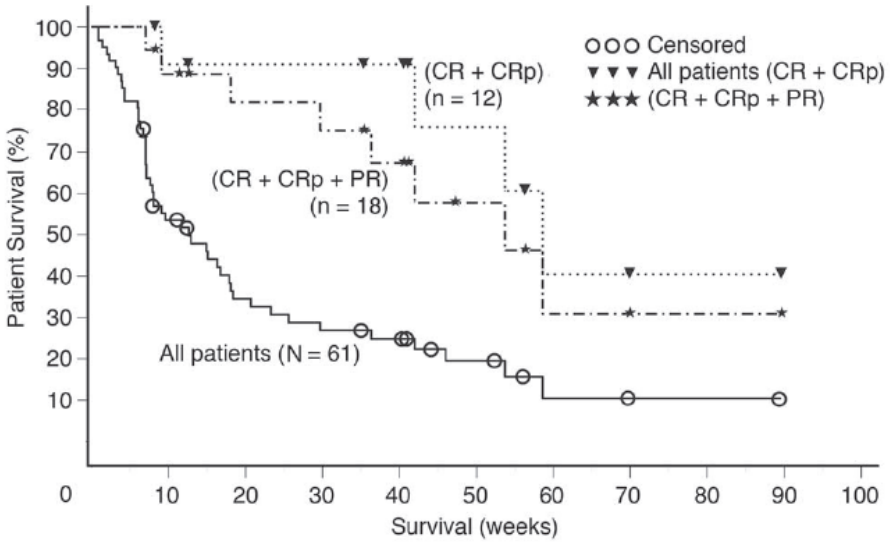
Six studies evaluating clofarabine were identified. Studies that had an OS of around 9 months were excluded and studies that evaluated clofarabine combination therapy rather than monotherapy were excluded. The ERG considers that excluding trials on this basis was not justifiable.

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

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

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

Figure 16 Kaplan-Meier curve for overall survival from Jeha *et al*. (2006)



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

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

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

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

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

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

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

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

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

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

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

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

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

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

Figure 17 Overall survival for tisagenlecleucel-T versus blinatumomab

Figure 18 Overall survival for tisagenlecleucel-T versus salvage chemotherapy

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was carried out by the ERG.

4.6 Conclusions of the clinical effectiveness section

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

The ERG noted some limitations about the representativeness of the patients recruited to the trials. All three trials restricted eligibility to patients with a life expectancy of 12 weeks or more. Therefore, patients in these trials may be healthier and fitter than patients eligible for standard care in practice. The ERG recognises a delay between enrolment and infusion with tisagenlecleucel-T. The median time between enrolment and infusion of tisagenlecleucel-T in ELIANA, ENSIGN and B2101J was [redacted] days, 41 days and [redacted] days. This is substantially longer than the 3 to 4 weeks estimated in the CS, which has considerable implication for eligible patients due to the pace of disease progression and their short-estimated life expectancy.

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

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

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

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

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

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

5 Cost Effectiveness

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

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

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

5.1.1 Searches

The following databases were searched on 24 November 2017:

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

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

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

5.1.2 Inclusion/exclusion criteria used for study selection

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

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

5.1.3 Studies included and excluded in the cost effectiveness review

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

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

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

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

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

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

i) a short-term decision tree characterising the period from the initiation of treatment (CAR-T or chemotherapy) to the initial response assessment (approximately one month);
ii) a partitioned survival analysis model characterising the time period between the initial response assessment and five-years
iii) a Markov model from five-years until death. In all four models patients who were alive and responding to treatment at five-years were assumed to be long-term survivors and effectively 'cured'. Mortality after five years was then based on the general population age- and gender-adjusted all-cause risks of mortality, with adjustments made for excess mortality (using a standardised mortality ratio).

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

5.1.4 Conclusions of the cost effectiveness review

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

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

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

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

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

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

Table 4 Overview of the company's economic evaluation

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

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

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

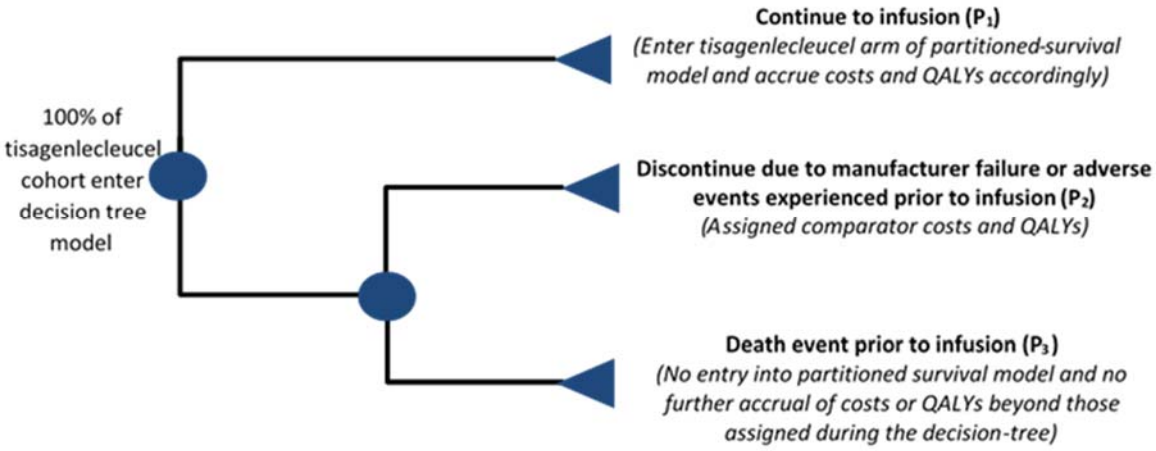
5.2.1 Model structure

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

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

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

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



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

Table 5 Patient proportions in the decision tree by pathway

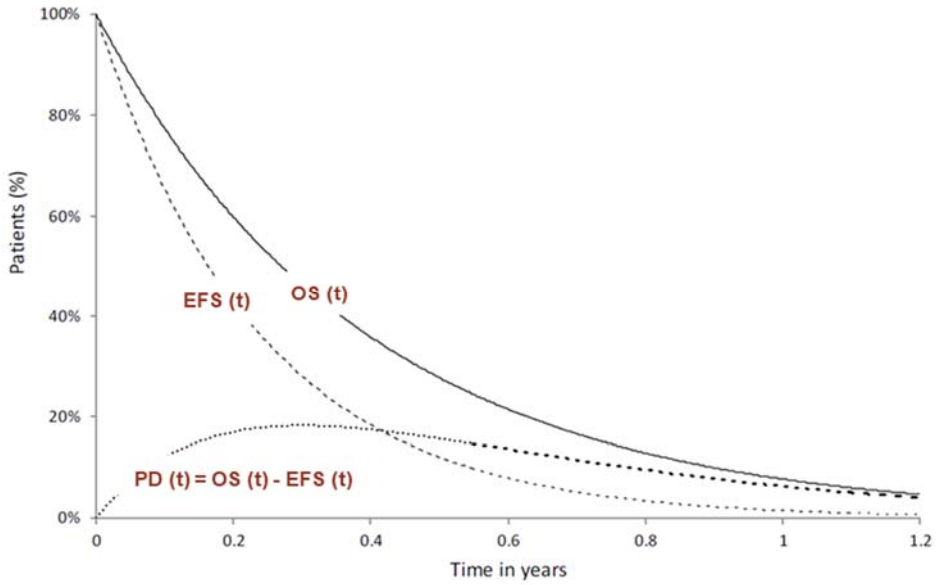
	Continue to infusion (P1)	**Discontinue prior to infusion (P2)**	**Die prior to infusion (P3)**
Proportion of patients who underwent leukapheresis	[redacted]%	[redacted]%	[redacted]%

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

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

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

Figure 20 Partitioned survival modelling approach (presented in the CS Figure 26; pg. 94)



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

ERG comment

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

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

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

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

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

Figure 21 Kaplan-Meier curve for OS for patients not infused with tisagenlecleucel-T in ELIANA (Clarification response, fig 33)

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

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

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

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

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

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

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

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

5.2.3 Population

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

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

ERG comment

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

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

5.2.4 Interventions and comparators

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

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

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

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

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

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

ERG comment

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

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

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

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

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

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

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

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

5.2.5 Perspective, time horizon and discounting

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

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

5.2.6 Treatment effectiveness and extrapolation

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

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

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

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

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

Figure 22 Kaplan-Meier and parametric extrapolations of overall survival for tisagenlecleucel-T

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

5.2.6.1 Uncontrolled comparison of treatment effectiveness

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

Blinatumomab

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

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

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

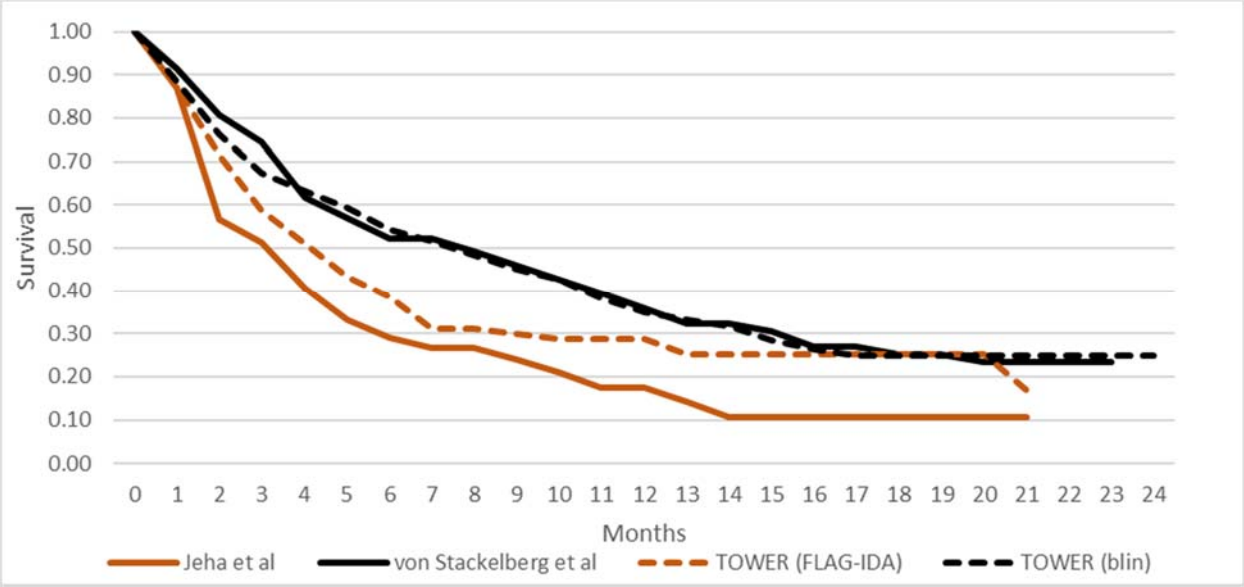
FLA-IDA

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

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

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

Figure 23 Comparison of Jeha, von Stackelberg and Tower trial OS curves



In response to the limitations of the evidence by the company, the ERG performed a limited literature search for further evidence on the prognosis of these patients. These searches identified two relevant studies, both of which were published after the company's searches were undertaken.

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

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

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

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

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

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

5.2.6.2 Overall survival

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

Tisagenlecleucel

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

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

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

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

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

Figure 24 Extrapolation of tisagenlecleucel-T overall survival using mixture cure models (CS Figure 19, Page 109)

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

ERG Comment

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

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

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

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

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

Blinatumomab

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

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

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

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

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

ERG Comment

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

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

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

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

FLA-IDA

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

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

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

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

ERG Comment

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

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

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

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

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

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

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

5.2.6.3 Event free survival

Tisagenlecleucel

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

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

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

[redacted]

Comparator regimens

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

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

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

ERG Comment

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

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

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

5.2.7 Adverse events

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

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

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

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

ERG Comment

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

5.2.8 Health related quality of life

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

5.2.8.1 Systematic review of utilities and HRQoL

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

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

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

5.2.8.2 Health state utilities

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

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

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

Table 8 Summary of utility values applied in model and scenarios

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

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

The utility values for event-free survival and long-term survival used by Kelly and colleagues were derived from a Swiss study [58] which generated SF-36 scores for patients diagnosed with ALL between 1976 and 2003, who had been cured following relapse and had survived for at least 5 years. These utility values are based on HUI2, rather than EQ-5D. While the company explains the utility value applied for LTS is based on patients in EFS, this is in fact derived from long-term (≥5 years) survivors. It is uncertain whether the utility of cured patients is equivalent to those in short-term EFS, particularly as the 0.91 value was conditional on >5 years of survival, this study is likely to have excluded the majority of those who initially achieved remission but later relapsed. In Section 6 the ERG presents a scenario using EFS and PD utility values obtained from ELIANA, with the LTS value from Kelly *et al*. to more accurately reflect their respective sources.

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

5.2.8.3 Treatment and adverse event disutilities

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

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

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

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

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

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

5.2.9 Resources and costs

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

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

5.2.9.1 Cost of delivering tisagenlecleucel

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

Pre-treatment costs

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

Table 9 Summary of pre-treatment costs

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

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

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

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

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

Infusion with tisagenlecleucel

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

Table 10 Summary of costs associated with tisagenlecleucel

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

ERG comment

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

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

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

5.2.9.2 Cost of comparator therapies

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

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

Salvage therapy								
Treatment	**Cost per vial**		**Dose**		**Average dose per infusion**	**Vials per infusion**	**Infusions per cycle**	**Total drug cost**	**Total admin cost**
Fludarabine	£23.01 (50 mg)		30 mg/m^2 daily		37.8 mg	1	5	£115.05	£16,214.30
Cytarabine	£6.13 (1000 mg)		2 mg/m^2 daily		2520.0 mg	3	5	£91.95	
Idarubicin	£87.36 (5 mg)		8 mg/m^2 daily		10.08 mg	3	3	£786.24	
Total cost								**£993.24**	**£16,214.30**
Blinatumomab									
Cycle	**Dose**		**Average dose per infusion**		**Vials per infusion**	**Infusions per cycle**	**Distribution of patients per cycle**	**Total drug cost**	**Total admin cost**
	Child	**Adult**	**Child**	**Adult**					
Cycle 1 (days 1–7)	5 mcg/m^2/day	9 mcg /day	5.95	9.00	1.00	7	96%	£54,055.60	£10,749.50
Cycle 1 (days 8–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	21			
Cycle 2 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	31%	£17,749.60	£3,251.91
Cycle 3 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	10%	£5,647.60	£585.15
Cycle 4 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	4%	£2,420.40	£250.78
Cycle 5 (days 1–28)	15 mcg/m^2/day	28 mcg /day	17.86	28.00	1.00	28	4%	£2,420.40	£250.78
Total cost								**£82,293.60**	**£13,731.41**

Salvage chemotherapy

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

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

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

Blinatumomab

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

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

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

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

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

ERG comment

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

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

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

5.2.9.3 Monitoring and follow-up

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

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

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

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

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

ERG comment

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

5.2.9.4 Allo-SCT costs

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

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

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

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

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

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

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

ERG comment

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

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

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

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

5.2.9.5 Adverse event costs

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

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

Cytokine release syndrome

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

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

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

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

B-cell aplasia

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

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

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

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

ERG comment

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

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

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

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

5.2.9.6 Costs of terminal care

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

ERG comment

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

5.2.10 Cost effectiveness results

5.2.10.1 Base case results

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

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

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

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

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

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

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

5.2.10.2 Sensitivity analyses

Probabilistic sensitivity analysis

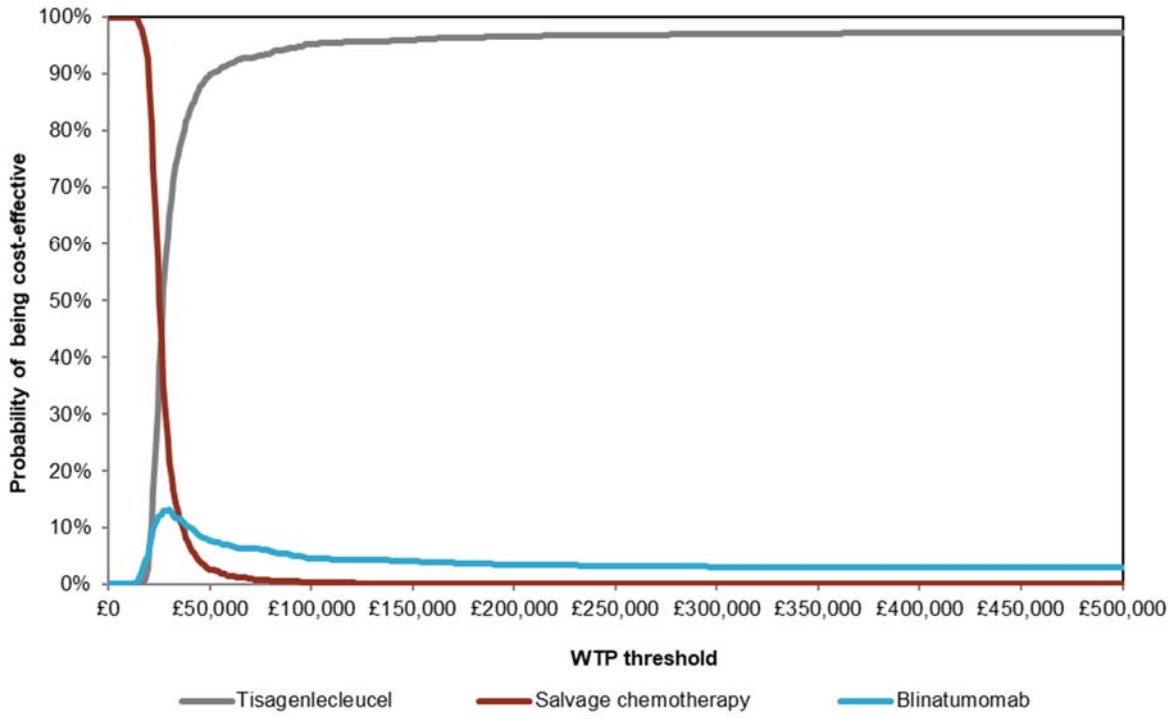
The company performed a probabilistic sensitivity analysis (PSA) using Monte-Carlo simulation with 2,000 iterations. In each iteration, the model drew inputs from defined distributions for selected parameters (CS Table 63, Pages 159-162), and efficacy inputs were modelled using parametric estimates of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

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

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

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

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



WTP, willingness-to-pay

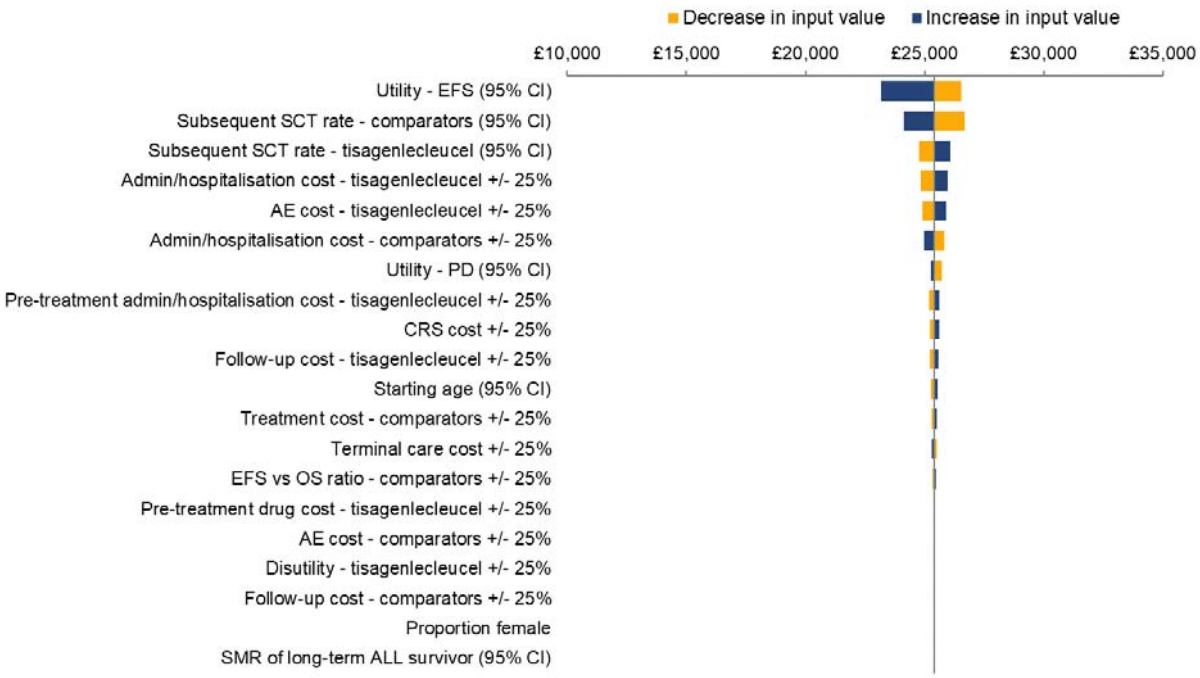
Compared to the deterministic analysis, the results of the PSA differed significantly in total QALYs, with small differences in costs. The average incremental QALYs gained with tisagenlecleucel-T compared to salvage chemotherapy were [redacted], which was [redacted] QALYs fewer than in the deterministic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

Deterministic sensitivity analyses

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

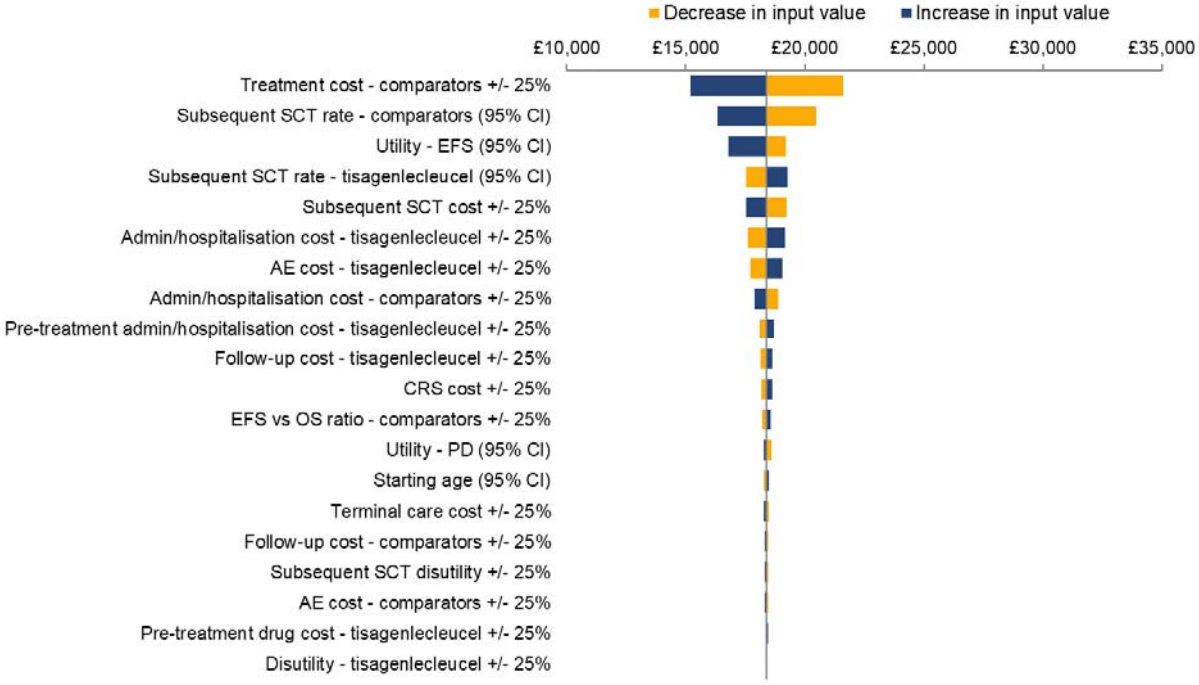
Table 66. Tornado diagrams summarising the twenty most influential parameters as reported by the company are presented in Figure 28 (versus salvage chemotherapy) and Figure 29 (versus blinatumomab). The results indicate that varying the utility values associated with EFS, and the rates of subsequent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

Figure 28 Tornado diagram of the 20 most influential DSA parameters (tisagenlecleucel-T [inc. PAS] vs. FLA-IDA) (CS, Figure 48, Page 170)



Key: AE, adverse event; CRS, cytokine release syndrome; DSA, deterministic sensitivity analysis; EFS, event-free survival; FLA-IDA, fludarabine, cytarabine and idarubicin; PAS, patient access scheme; PD, relapsed/progressed disease; SCT, stem cell transplant.

Figure 29 Tornado diagram of the 20 most influential DSA parameters (tisagenlecleucel-T [inc. PAS] vs. blinatumomab) (CS, Figure 49, Page 170)



Key: AE, adverse event; CRS, cytokine release syndrome; DSA, deterministic sensitivity analysis; EFS, event-free survival; PAS, patient access scheme; PD, relapsed/progressed disease; SCT, stem cell transplant.

Scenario analysis results

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

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

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

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

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

5.2.11 Model validation and face validity check

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

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

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

5.3 Conclusions of the cost effectiveness section

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

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

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

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

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

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

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

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

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

The ERG highlights the uncertainty regarding the treatment of patients with 2+ relapses in the NHS. Firstly, NICE guidance is already in place for the ~8.3% of patients aged >18 years, who would typically receive blinatumomab as a first-line salvage therapy. This means this population would not be eligible for blinatumomab again after a second relapse, as considered in this appraisal. Clinical advice to the ERG and company suggests this is increasingly becoming the case in paediatric patients; as blinatumomab is used earlier in the treatment pathway, it may be that FLA-IDA is the most relevant comparator for patients with two or more relapses. However, the ERG notes that this is a rapidly evolving field, and other drugs such as inotuzumab and daratumumab are also being used at this point in the treatment pathway.

The ERG also considers the impact of blinatumomab use earlier in the treatment pathway to raise the issue of eligibility for tisagenlecleucel-T after 2+ relapses. A key exclusion criterion of the three tisagenlecleucel-T trials was the previous use of an anti-CD19 therapy such as blinatumomab, due to the hypothetical impact upon treatment efficacy and the chance of CD19-negative relapse, which was observed in 22% of tested relapses in the paediatric blinatumomab trial. This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy. The ERG considers that CD19 expression would need to be quantified before patients could be considered for treatment with tisagenlecleucel-T, as patients with weak or no expression of CD19 would gain little to no benefit from this treatment.

4) Identification and selection of appropriate comparator data source

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

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

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

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

6) Uncertainty surrounding broader infrastructure and training requirements

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

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

1) Treatment of B-cell aplasia

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

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

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

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

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

6.1 Overview

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

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

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

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

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

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

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

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

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

6.3 Additional ERG analyses

6.3.1 Modelling patients who did not receive infusion with tisagenlecleucel

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3.2 Cure models applied to salvage chemotherapy OS data

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

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

Figure 30 Top three fitting mixture-cure models for salvage chemotherapy studies Jeha (A), Hijaya (B), Locatelli (C))

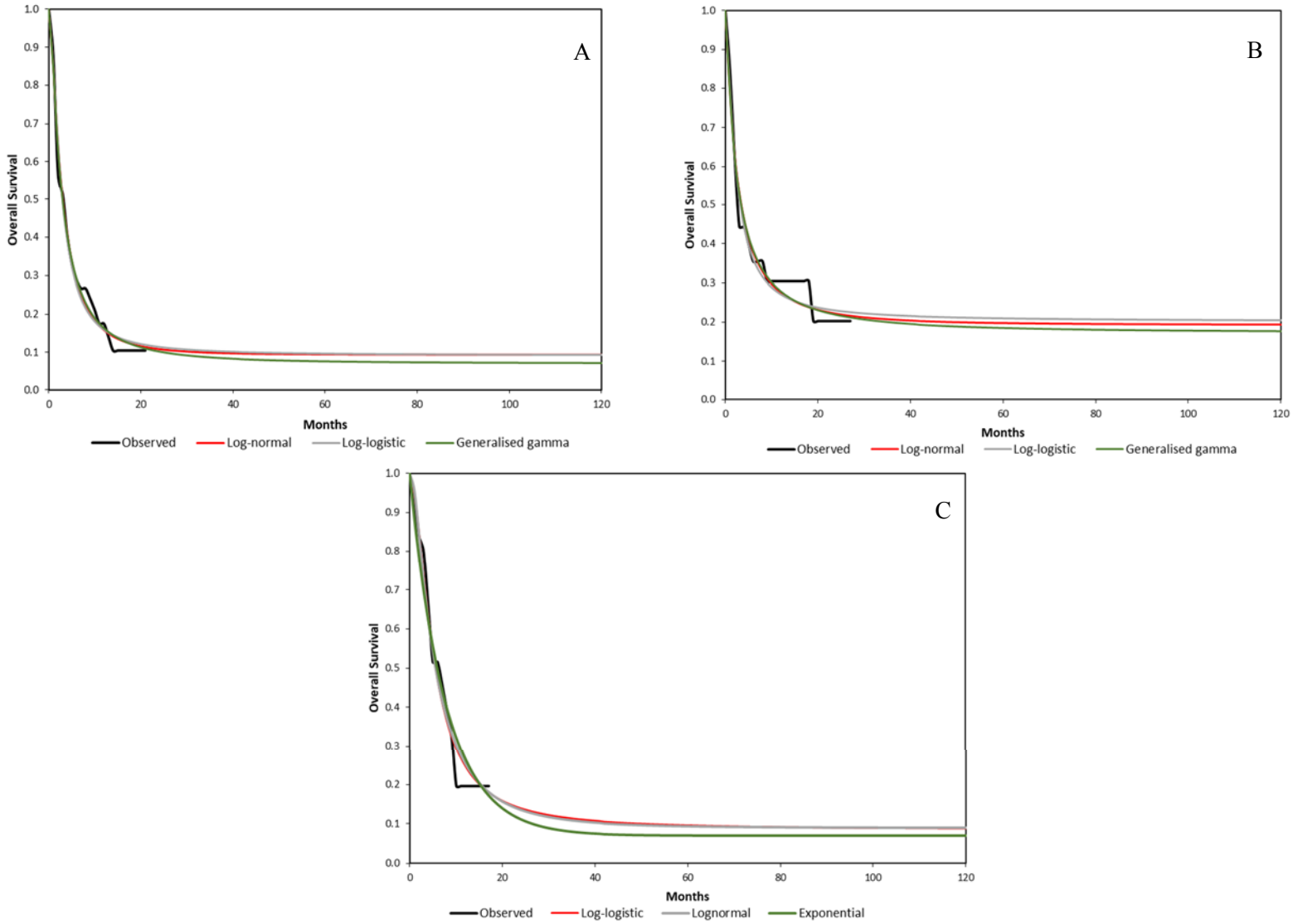


Table 21 Cure modelling approach for salvage chemotherapy (tisagenlecleucel-T PAS price)

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

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

6.3.3 Kuhlen *et al.* data for salvage chemotherapy

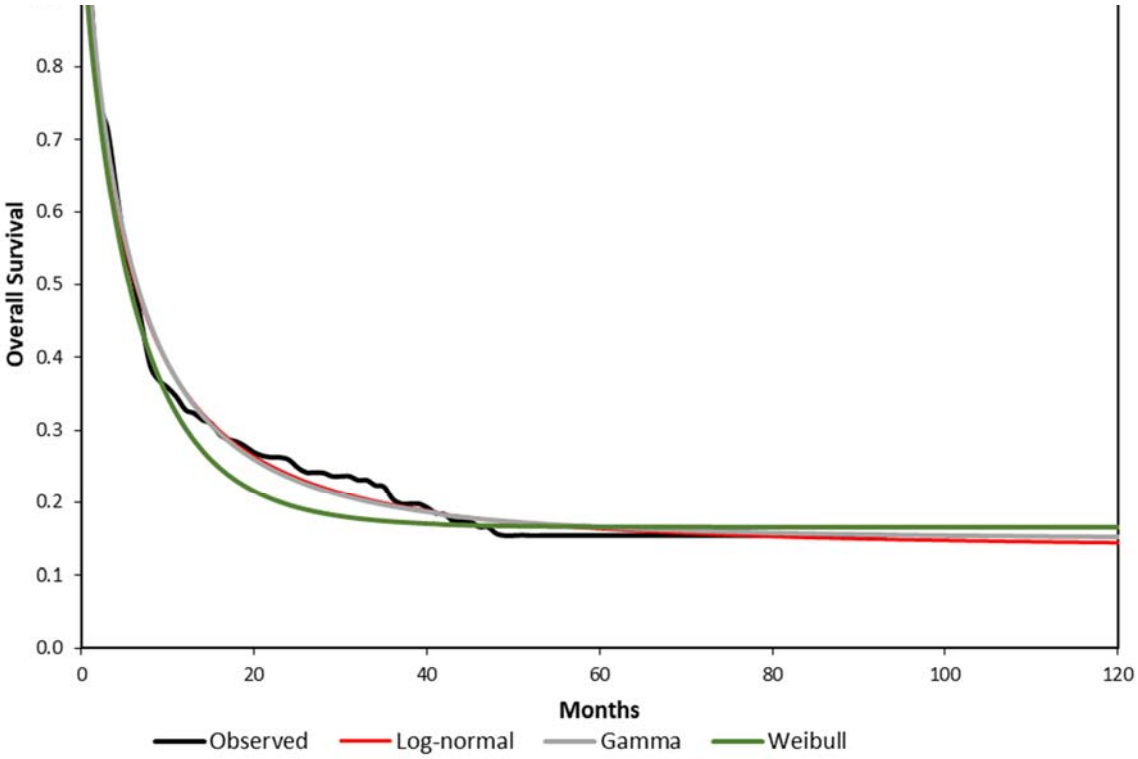
The ERG identified an alternative source of evidence on the prognosis of patients on salvage therapy, Kuhlen *et al.* (2017) [12], which was felt to be at least as plausible as the trials identified by the company to represent survival of patients receiving salvage therapy. As discussed in Section 5.2.6,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

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

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

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

Figure 31 Top three fitting mixture-cure models for Kuhlen *et al.* OS data



In this scenario, adverse event rates for salvage therapy were based on those reported by Kantarjian *et al.* (2017), and rates of SCT were extracted from Kuhlen *et al.* (2017), where 61 of 173 (35%) patients who received salvage therapy in the trial received subsequent SCT.

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

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

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

6.3.4 Prevalence and duration of IVIG use

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

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

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

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

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

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

6.3.5 Stem-cell transplant prevalence and utility

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

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

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

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

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

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

6.3.6 Duration of treatment with blinatumomab

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

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

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

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

6.3.7 Usage of ICU beds for patients with cytokine release syndrome

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

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

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

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

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

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

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

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

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

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

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

6.4 ERG alternative base-case

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

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

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

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

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

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

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

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

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

6.5 Exploratory analyses on ERG alternative base-case

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

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

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

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

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

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

			Incremental results			
Comparator	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**ΔICER from ERG BC**
ERG deterministic base-case						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£45,397	-
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£27,732	-
ERG base-case: 0% of tisagenlecleucel-T patients receive SCT						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£41,274	-£4,122
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£23,900	-£3,831
ERG base-case: 100% of patients in EFS receive SCT						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£65,229	£19,833
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£46,133	£18,401
ERG base-case: 3-year duration of IVIG use in patients with HGG						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£48,475	£3,079
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£30,695	£2,963
ERG base-case: IVIG use based on ongoing HGG in patients in EFS						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£58,342	£12,945
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£40,192	£12,460
ERG base-case: tisagenlecleucel-T OS based on lognormal cure model						
Tisagenlecleucel	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£74,322	£28,925
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£44,299	£16,567

Key: HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; PAS, patient access scheme; QALYs, quality-adjusted life year; SCT, stem cell transplant

6.6 Conclusions from ERG analyses

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

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

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

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

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

7 End of life

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

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

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

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

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

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

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

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

8 Overall conclusions

Clinical effectiveness

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

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

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

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

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

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

Cost effectiveness

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

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

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

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

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

8.2 Implications for research

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

9 References

1. Children with Cancer UK. *Acute Lymphoblastic Leukaemia in Children*. Available from: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/acute-lymphoblastic-leukaemia/ [accessed 16th May 2018].

2. Cancer Research UK. *Acute lymphoblastic leukaemia (ALL) incidence statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero [accessed 16th May 2018 2018].

3. American Cancer Society. *How is childhood leukemia classified?* Available from: https://www.cancer.org/cancer/leukemia-in-children/detection-diagnosis-staging/how-classified.html [accessed 16th May 2018].

4. 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.

5. Ceppi F, Duval M, Leclerc JM, Laverdiere C, Delva YL, 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**:e0160310. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27632202

6. 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* 2010;**28**:648-54. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19841326

7. 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**:1917-23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16622268

8. 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**:4381-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27998223

9. 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. *Br J Haematol* 2009;**147**:371-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19747360

10. 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**:285-90. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22653976

11. European Medicines Agency. *Blincyto. Summary of product characteristics*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003731/WC500198228.pdf

12. 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. *Br J Haematol* 2017;**180**:82-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29193007

13. Leukaemia Foundation. What is acute lymphoblastic leukaemia? https://www.leukaemia.org.au/disease-information/leukaemias/acute-lymphoblastic-leukaemia/.

14. NHS Choices. *Acute lymphoblastic leukaemia*. Available from: https://www.nhs.uk/conditions/acute-lymphoblastic-leukaemia/#symptoms [accessed 16th May 2018].

15. American Cancer Society. *What is acute lymphocytic eukemia?* 2016. Available from: https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html [accessed 16th May 2018].

16. Dana-Farber/Boston Children's Cancer and Blood Disorders Center. *Relapsed Acute Lymphoblastic Leukemia (ALL)*. Available from: http://www.danafarberbostonchildrens.org/conditions/leukemia-and-lymphoma/relapsed-acute-lymphoblastic-leukemia.aspx[16/05/2018 16:57:15] [accessed 16th May 2018].

17. Cancer Research UK. *About acute lymphoblastic leukaemia (ALL)*. Available from: http://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [accessed 16th May 2018].

18. Cancer Research UK. *Acute lymphoblastic leukaemia (ALL) incidence statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-One [accessed 16th May 2018].

19. Nguyen K, Devidas M, Cheng SC, 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**:2142-50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18818707

20. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *J Clin Oncol* 2015;**33**:2938-48. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26304874

21. Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, et al. Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia. *Leukemia* 2017;**32**:606. Available from: http://dx.doi.org/10.1038/leu.2017.265

22. Miano M, Pistorio A, Putti M, Dufour C, Messina C, Barisone E, et al. Clofarabine, cyclophosphamide and etoposide for ther treatment of relapsed or resistant acute leukemia in pediatric patients. *Leuk Lymphoma* 2012;**53**:1693-8.

23. 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**:6043-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21967976

24. 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. *Pediatr Blood Cancer* 2013;**60**:1141-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23335239

25. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. *Pediatr Clin North Am* 2015;**62**:61-73. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25435112

26. Pulsipher MA, Peters C, Pui CH. High Risk Pediatric Acute Lymphoblastic Leukemia: To Transplant or Not to Transplant? *Biol Blood Marrow Transplant* 2011;**17**:S137-48.

27. Sellar RS, Rowntree C, Vora AJ, Furness CL, Goulden N, Mitchell C, et al. Relapse in teenage and young adult patients treated on a paediatric minimal residual disease stratified ALL treatment protocol is associated with a poor outcome: results from UKALL2003. *Br J Haematol* 2018;**181**:515-22.

28. Macmillan Cancer Support. *Hyper-CVAD chemotherapy*. Available from: https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/combinationregimen/hyper-cvad.aspx [accessed 16th May 2018].

29. Reinfjell T, Lofstad GE, Nordahl HM, Vikan A, Diseth TH. Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. *Eur J Cancer Care (Engl)* 2009;**18**:364-70. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19473372

30. (NOPHO) NSoPHaO. NOPHO-ALL 2008 Final protocol version 3a: Treatment Protocol for Children (1.0 - 17.9 years of age) and young adults

(18-45 years of age) with Acute Lymphoblastic Leukemia. 2011.

31. National Cancer Institute. Childhood Acute Lymphoblastic Leukemia Treatment 2018. Available from: https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq

32. National Institute for Health and Care Excellence. *Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]. Final scope*. London: NICE; 2018. Available from: https://www.nice.org.uk/guidance/gid-ta10270/documents/final-scope

33. U.S. Food & Drug Administration. *FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome*. 2017. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574154.htm [accessed 16th May 2018].

34. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology. Am Soc Hematol Educ Program* 2010:7-12.

35. 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 & specialty pharmacy* 2016;**22**:1107-13.

36. Major B. Initial experience in us commercial manufacturing of tisagenlecleucel, a chimeric antigen receptor (car)-t cell therapy for pediatric relapsed/refractory b-cell precursor acute lymphoblastic leukemia. *European Hematology Association* 2018;**215467**. Available from: https://learningcenter.ehaweb.org/eha/2018/stockholm/215467/brian.majors.initial.experience.in.us.commercial.manufacturing.of.html?f=menu=6*ce_id=1346*ot_id=19055*media=3*marker=167

37. Rowe JM. Prognostic factors in adult acute lymphoblastic leukaemia. *Br J Haematol* 2010;**150**:389-405.

38. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health* 2012;**15**:940-7.

39. Hao Y, Eldjerou LK, Yang H, Qi C, Globe D. Cost-effectiveness analysis of CTL019 for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia in the United States. *Blood* 2017;**130**:609.

40. 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 Technol Assess* 2017;**21**:1-204. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28244858

41. Review IfCaE. *Chimeric antigen receptor T-cell therapy for B-cell cancers: effectiveness and value. Draft evidence report*. Boston, MA: ICER; 2017. Available from: https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf

42. Snider J, Brauer M, Hao Y, Karaca-Mandic P, Gizaw Tebeka M, Zhang J, et al. The economic value of CTL019 therapy for pediatric patients with relapsed and refractory acute lymphoblastic leukemia in the United Kingdom. *Blood* 2017;**130**:1330.

43. National Institute for Health and Clinical Excellence. *Blinatumomab for treating Philadelphiachromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]. Committee papers*; 2017. Available from: https://www.nice.org.uk/guidance/ta450/documents/committee-papers

44. National Institute for Health and Clinical Excellence. *Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]. Committee papers*. London: NICE; 2018. Available from: https://www.nice.org.uk/guidance/GID-TA10091/documents/committee-papers-3

45. Winters ABK. MLL-Rearranged Leukemias—An Update on Science and Clinical Approaches. *Frontiers in Pediatrics* 2017;**5**.

46. Mejstríková EH, O; Borowitz, MJ; Whitlock, JA; Brethon, B; Trippett, TM; Zugmaier, G; Gore, L; von Stackelberg, A; Locatelli, F. CD19-negative relapse of pediatric B-cell precursor acute lymphoblastic leukemia following blinatumomab treatment. *Blood Cancer Journal* 2017;**7**.

47. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. London: NICE; 2013.

48. National Insttitue for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. London: NICE; 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781

49. *Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (ELIANA)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02435849 [accessed 16th May 2018].

50. Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 2017;**376**:836-47. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28249141

51. Locatelli F, Zugmaier G, Vora A, Rossig C, Peters C, Brethon B. Blinatumomab use in pediatric patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) from an open-label, multicenter, expanded access study. *J Clin Oncol* 2017;**35**:10530.

52. Ltd NP. 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). 2017.

53. Lambert PT, JR; Weston, CL; Dickman, PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics* 2007;**8**:576-94.

54. Yu BT, RC; Cronin KA; Feuer EJ. Cure fraction estimation from the mixture cure models for grouped survival data. *Stat Med* 2004;**23**:1733-47.

55. 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**:2009-17.

56. 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. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25755144

57. 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 Qual Life Outcomes* 2015;**13**:181. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26573610

58. Essig SvdW, NX; Strippoli, M-PF; Rebholz, CE; Michel, G; Rueegg, CS; Niggli, FK; Kuehni, CE. Health-Related Quality of Life in Long-Term Survivors of Relapsed Childhood Acute Lymphoblastic Leukemia. *PLoS ONE* 2012;**7**.

59. Szende A, Janssen B, Cabase´s J, editors. *Self-reported population health: an international perspective based on EQ-5D*. Dordrecht: Springer, 2014.

60. 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**:592-600. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12548601

61. Felder-Puig RdG, A; Waldenmair, M; Norden, P; Winter, A; Gadner, H; Topf, R. 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 Transplant* 2006;**38**:119-26.

62. Grulke NA, C; Bailer, H. . Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant* 2012;**47**:473-82.

63. Peric ZD, L; Durakovic, N. *et al*. Which questionnaires should we use to evaluate quality of life in patients with chronic graft-vs-host disease? *Croat Med J* 2016;**57**:6-15.

64. Kurosawa SY, H; Yamaguchi, T; Fukunaga, K; Yui, S; Kanamori, H; Usuki, K; Uoshima, N; Yanada, M; Shono, K; Ueki, T; Mizuno, I; Yano, S; Takeuchi, J; Kanda, J; Okamura, H; Tajima, K; Inamoto, Y; Inokuchi, K; Fukuda, T. Decision Analysis of Allogeneic Hematopoietic Stem Cell Transplantation Versus Chemotherapy in Cytogenetically Standard-Risk Acute Myeloid Leukemia in First Complete Remission: The Impact of FLT3-ITD Profile. *Blood* 2014;**124**.

65. Department of Health. *Reference Costs 2016-17*. London: DoH; 2017. Available from: https://improvement.nhs.uk/resources/reference-costs/

66. Department of Health. *Drugs and pharmacuetical electronic market information (eMit)*. 2011. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [accessed 6th December 2017].

67. Perica K, Curran K, Brentjens R, Giralt S. Building a CAR garage: preparing for the delivery of commercial CAR T cell products at Memorial Sloan Kettering Cancer Center. *Biol Blood Marrow Transplant* 2018;**24**:1135-41.

68. Neelapu SS, Tummala S, P K, Wierda W, Gutierrez C, Locke F, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nature Reviews Clinical Oncology* 2018;**15**:47.

69. British National Formulary. *Idarubicin*. Available from: https://bnf.nice.org.uk/medicinal-forms/idarubicin-hydrochloride.html [accessed 16th May 2018].

70. NHS Thames Valley Strategic Clinical Network. *FLA-IDA*; 2017.

71. British National Formulary. *Blinatumomab*. Available from: https://bnf.nice.org.uk/medicinal-forms/blinatumomab.html [accessed 16th May 2018].

72. National Comprehensive Cancer Network. *Acute lymphoblastic leukemia*; 2017. Available from: https://www.nccn.org/patients/guidelines/all/index.html

73. Campbell K. *Childhood acute lymphoblastic leukaemia (ALL) and teenagers and young adults up to 24 years old*; 2011. Available from: http://leukaemialymphomaresearch.org.uk/sites/default/files/childhood_all_oct_2011.pdf

74. Barredo JC, Hastings C, Lu X, Devidas M, Chen Y, Armstrong D, et al. Isolated late testicular relapse of B-cell acute lymphoblastic leukemia treated with intensive systemic chemotherapy and response-based testicular radiation: A Children's Oncology Group study. *Pediatr Blood Cancer* 2018;**65**:e26928. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29286562

75. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010;**28**:935-45.

76. NHS Blood and Transplant. *Unrelated donor stem cell transplantation in the UK: effective affordable sustainable. A report from the UK Stem Cell Strategy Oversight Committee November 2014*: NHSBT; 2014. Available from: http://docplayer.net/7404866-Unrelated-donor-stem-cell-transplantation-in-the-uk.html

77. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury: Personal Social Services Research Unit, University of Kent; 2017. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/

78. van Agthoven M, Groot M, Verdonck L, Löwenberg B, Schattenberg A, 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 Transplant* 2002;**30**:243-51.

79. British National Formulary. *Tocilizumab*. Available from: https://bnf.nice.org.uk/medicinal-forms/tocilizumab.html [accessed 16th May 2018].

80. British National Formulary. *Normal immunoglobulin* 16th May 2018. Available from: https://bnf.nice.org.uk/medicinal-forms/normal-immunoglobulin.html

81. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med* 2016;**374**:833-42. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26761625

82. Bhatia S, Robison LL, Francisco L, Carter A, Liu Y, Grant M, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. *Blood* 2005;**105**:4215-22. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15701723

83. Socié G, Stone J, Wingard J, Weisdorf D, Henslee-Downey P, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med* 1999;**341**:14-21.

84. von Stackelberg A, Völzke E, Kühl J, Seeger K, Schrauder A, Escherich G, et al. Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: a retrospective analysis of the ALL-REZ BFM Study Group. *Eur J Cancer* 2011;**47**:90-7.

85. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22297116

10 Appendices

10.1 Baseline characteristics of the full ITT population

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

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

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

10.2 Time to B-cell recovery

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

Figure 33 Kaplan-Meier curve for time to B-cell recovery in peripheral blood in patients who achieved CR or CRi in ENSIGN

10.3 Kaplan-Meier curves for OS all clofarabine combination trials

Figure 34 Kaplan-Meier curve for OS from Cooper *et al.* (2013)

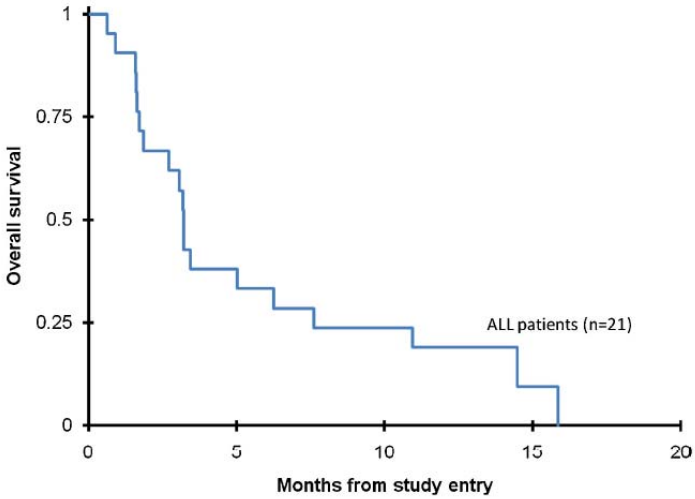


Figure 35 Kaplan-Meier curve for overall survival from Hijiya *et al.* (2011)

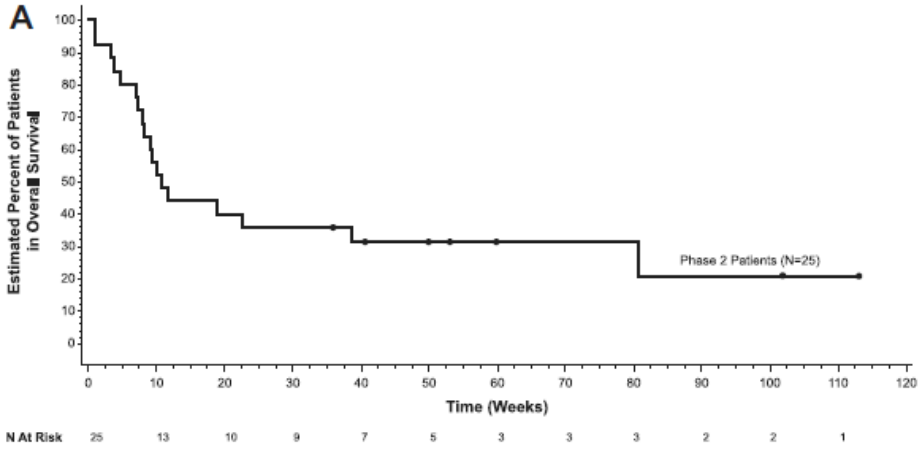


Figure 36 Kaplan-Meier curve for overall survival from Messinger *et al*. (2012)

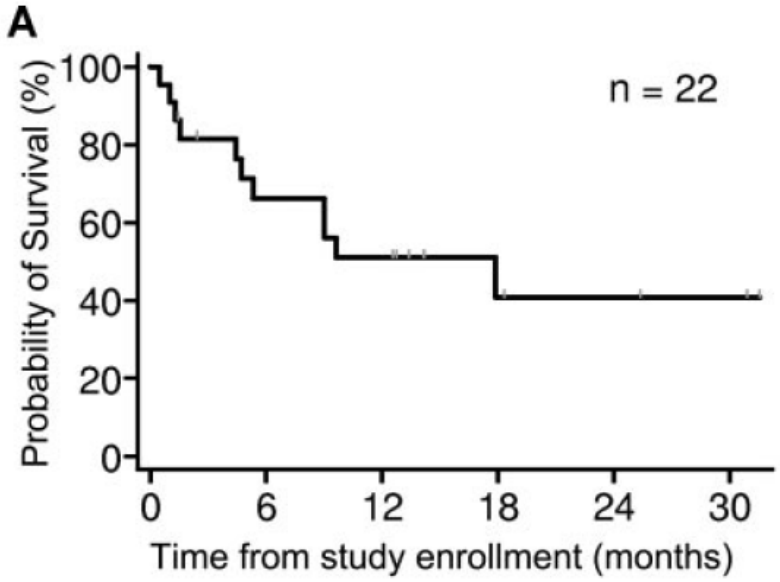
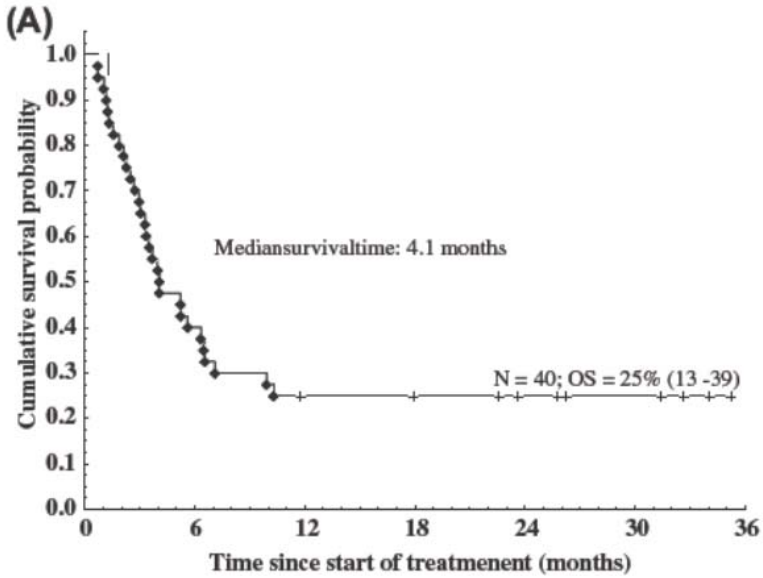


Figure 37 Kaplan-Meier curve for OS from Miano *et al*. (2012)



ADDENDUM
Evidence Review Group's Report

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

ERG base-case results incorporating alternative discount rate and confidential PAS discount for tisagenlecleucel-T

1 Impact of additional clinical and economic analyses undertaken by the ERG (with confidential PAS for tisagenlecleucel).

This addendum presents results of the ERG's alternative base-case incorporating a 1.5% discount rate, and a further scenario which examines the impact of TOWER as a source of adverse event rates. The results in this section reflect the outcome of analyses when the confidential PAS discount for tisagenlecleucel is applied.

This document contains three sections:

1.1 ERG base-case analysis

1.2 ERG base-case model: exploratory analyses

1.3 ERG corrected company base-case with TOWER adverse event rates

1.1 ERG base-case analysis

Addendum Table 1 presents the summary cost-effectiveness results of the company's base-case model with ERG corrections and a 1.5% discount rate applied, and Addendum Table 2 presents the results of the ERG alternative base-case model with a 1.5% discount rate. These tables include the PAS discount for tisagenlecleucel of [redacted]

Table 1 Results of the Company's base-case model (1.5% discount rate, tisagenlecleucel PAS price)

				Incremental results			
Comparator	**Costs**	**LYG**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Company base-case (3.5% discount rate)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392
Company base-case with ERG corrections and 1.5% discount rate							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,338
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,666
Key: ICER, incremental cost-effectiveness ratio; LYG, life-years gained, PAS, patient access scheme; QALYs, quality-adjusted life-years							

Table 2 Results of the ERG's base-case model (1.5% discount rate, tisagenlecleucel PAS price)

				Incremental results			
Comparator	**Costs**	**LYG**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
ERG's base-case model (3.5% discount rate)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,397

Blinatumomab	[redacted]						£27,732
ERG's base-case model (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£32,086
Blinatumomab	[redacted]						£19,516
ERG's probabilistic base-case model (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£34,732
Blinatumomab	[redacted]						£21,428
Key: ICER, incremental cost-effectiveness ratio; LYG, life-years gained, PAS, patient access scheme; QALYs, quality-adjusted life-years							

1.2 ERG base-case model: exploratory analyses

Addendum Table 3 presents the results of several scenarios on the ERG's alternative base-case with a 1.5% discount rate applied.

Table 3 Alternate ERG base-case assumptions (1.5% discount rate, tisagenlecleucel PAS price)

Comparator				**Incremental results**			
	Costs	**LYG**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
ERG's alternative deterministic base-case (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£32,086
Blinatumomab	[redacted]						£19,516
ERG base-case: 0% of tisagenlecleucel-T patients receive SCT (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£29,250
Blinatumomab	[redacted]						£16,871
ERG base-case: 100% of patients in EFS receive SCT (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£45,546
Blinatumomab	[redacted]						£32,052
ERG base-case: 3-year duration of IVIG use in patients with HGG (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£34,256
Blinatumomab	[redacted]						£21,593
ERG base-case: IVIG use based on ongoing HGG in patients in EFS (1.5% discount rate)							
Tisagenlecleucel	[redacted]						
Salvage Chemotherapy	[redacted]						£45,123
Blinatumomab	[redacted]						£31,988

Key: EFS, event-free survival; HGG, hypogammaglobulinaemia; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; LYG, life-years gained; OS, overall survival; PAS, patient access scheme; QALYs, quality-adjusted life-years; SCT, stem cell transplant

1.3 ERG corrected company base-case with TOWER adverse event rates

Addendum Table 4 presents the results of the ERG-corrected company base-case with adverse event rates derived from the TOWER trial applied to salvage chemotherapy data from Jeha *et al.* This scenario uses a 3.5% discount rate and applies only the PAS discount for tisagenlecleucel.

Table 4 ERG corrected company base-case including TOWER AE rates for salvage chemotherapy (tisagenlecleucel PAS price)

				Incremental results			
Comparator	**Costs**	**LYG**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Company base-case with ERG corrections (3.5% discount rate)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,806
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,864
Company base-case with ERG corrections and TOWER AE rates (3.5% discount rate)							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
Salvage Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,928
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,854
Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; LYG, life-years gained, PAS, patient access scheme; QALYs, quality-adjusted life-years							

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 6 July 2018** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Dear Stephanie,

Thank you for the opportunity to review the ERG report for factual inaccuracies. Further to this, please find below a summary of our *key* findings with further details of all our findings provided in the subsequent pages of this pro-forma. We hope these clarifications will be considered by the ERG to ensure that data are interpreted appropriately and to ensure that the appropriate assumptions are made within the economic analysis.

Implications of blinatumomab usage on the place of tisagenlecleucel in the treatment pathway

The ERG raises concerns that the increasing use of blinatumomab in earlier lines of therapy may impact the use of tisagenlecleucel in the treatment pathway. However, this is unlikely to be an issue for paediatric ALL patients because, as described in the company submission, newly diagnosed paediatric ALL patients are treated with chemotherapy and this is usually followed by the ALLR3 protocol for patients that relapse following 1st line treatment. The introduction of tisagenlecleucel in the paediatric population is likely to influence the choice of prior therapies, and therefore blinatumomab is unlikely to be used in an earlier setting than tisagenlecleucel for paediatric patients. These patients constitute 92% of the licensed population for tisagenlecleucel, the remaining 8% being teenagers and young adults.

It has been suggested that blinatumomab may be used more frequently in the 2nd line setting for teenage and young adult ALL patients. CD19-negative relapse rates of up to 22% have been described, however, even if previous use of blinatumomab were an issue, which we don't believe it is, it would therefore only apply to a very small proportion of the licensed tisagenlecleucel patients i.e. potentially around 2%.

Interpretation of the Kuhlen study

In several places within the ERG report, the ERG state that the overall survival (OS) predicted in the Kuhlen study is likely to represent an under-estimate and that the majority of limitations would tend to favour tisagenlecleucel. This interpretation is misleading as it does not consider the full limitations of the study. In the Kuhlen study (which is a population with prior stem-cell transplant [SCT] as acknowledged by the ERG), 26.3% of patients received subsequent SCTs. Second SCTs are rare in the UK in this patient population, which raises questions about the representativeness of this study to UK practice. The high rate of subsequent SCT biases results against tisagenlecleucel as SCT is a curative option and therefore OS in this study is a clear overestimate. The HR for OS and EFS for T-ALL vs. B-ALL (Table II in the Kuhlen study) was also not statistically significant and therefore it is misleading to state that there is a difference in outcomes between these groups. In contrast, patients with extramedullary relapse were excluded from ELIANA (representing approximately 20% of the Kuhlen study population) which are shown to have statistically significantly better outcomes for both OS and event-free survival (EFS).

We kindly request that the ERG consider our comments in this response document and make the necessary amendments to their report.

Kind regards,

[redacted] Novartis Pharmaceuticals UK Ltd

Section 1: Major comments

Issue 1 Implications of blinatumomab usage on the place of tisagenlecleucel in the treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report the ERG refer to the potential use of blinatumomab earlier on in the treatment pathway and the potential for some patients to experience a CD-19 negative relapse, stating that: *'This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy.'* (Page 19) Further on Page 119, the ERG report states that *'The ERG considers that CD19 expression would need to be quantified before patients could be considered for treatment with tisagenlecleucel-T, as patients with weak or no expression of CD19 would gain little to no benefit from this treatment.'*	There is no evidence to suggest that patients with a CD-19 negative relapse would not respond to treatment with tisagenlecleucel (see justification for amendment). Novartis believe the following statements on Page 19 and Page 119 of the ERG report should be amended as follows: *'~~This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy.~~* ***It is not yet known how patients with a CD-19 negative relapse would respond to treatment with tisagenlecleucel.****'* Page 119: *'~~This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy. The ERG considers that CD19 expression would need to be quantified before patients could be considered for treatment with tisagenlecleucel-T, as patients with weak or no expression of CD19 would gain little to no benefit from this treatment.~~* ***It is not yet known how patients with a CD-19 negative relapse would respond to treatment with tisagenlecleucel.****'*	The ERG raises concerns that the increasing use of blinatumomab in earlier lines of treatment may impact the eligibility of tisagenlecleucel in the treatment pathway. However, this is unlikely to be an issue for paediatric ALL patients because, as described in the company submission, newly diagnosed paediatric ALL patients are treated with chemotherapy and this is usually followed by the ALLR3 protocol for patients that relapse following 1st line treatment. The availability of tisagenlecleucel in the paediatric population is likely to influence the choice of prior therapies, and therefore blinatumomab is unlikely to be used in an earlier setting than tisagenlecleucel for paediatric patients. These patients constitute 92% of the licensed population for tisagenlecleucel, the remaining 8% being teenagers and young adults. There is also no evidence to suggest that patients with a CD-19 negative relapse would not respond to treatment with tisagenlecleucel. There is no evidence to suggest that patients with weak or no	Not a factual error – clinical opinion which is being further explored in technical engagement.

		expression of CD-19 would not respond to treatment with tisagenlecleucel. This was tested as a protocol-defined exploratory analysis in the JULIET study (for DLBCL) and demonstrated no apparent difference in ORR or OS between CD19-positive and CD19-low/negative patients. It was concluded that there is no lower threshold level of CD19 expression in tumour tissue which could be set as basis to define CD19 positivity in the context of tisagenlecleucel therapy, or which could be considered as basis to justify exclusion of patients with unmeasurable CD19 levels from tisagenlecleucel treatment. As such, the use of blinatumomab earlier on in the treatment pathway would not preclude the use of tisagenlecleucel for the vast majority of the eligible patient population. Novartis therefore believe these statements from the ERG may be taken out of context here and should be amended as appropriate.	

Issue 2 Interpretation of the Kuhlen paper

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report, the ERG state that the overall survival predicted in the Kuhlen study is	On Page 80, it is proposed that the report should read, '*The Kuhlen et al. study, however, has a number of limitations. These*	The interpretation of the ERG does not consider the full limitations of the Kuhlen study in terms of both its	Not a factual error. The ERG report is very clear that the Kuhlen study is subject to

likely to represent an under-estimate and that the majority of limitations would tend to favour tisagenlecleucel (e.g. Page 80). However, Novartis feel this interpretation is misleading as it does not consider the full limitations of the study. Novartis therefore request that statements relating to the Kuhlen study are appropriately accompanied by full acknowledgement of the associated limitations. On Page 80, the ERG report states that: '*The second study, Kuhlen et al (2017) provides more complete survival data (n=242) for a period of up to 8 years, on patients recruited to two German paediatric ALL trials and who had relapsed following SCT'.* This statement is misleading with regards to the benefits of using the Kuhlen *et al.* study as the median follow up was 3.7 years, and the median follow up was 3.7 years, and the number of patients at risk after 4 years was very small. Finally, on Pages 25–26, the ERG makes reference to T-cell ALL patients having a poorer prognosis than B-cell ALL (based on Table II in the Kuhlen study); however, this result was not statistically significant and	*are described in Table 7 below, and includes a view on the likely direction of bias introduced by each limitation. The majority of these factors would tend to favour tisagenlecleucel-T; however, it is very difficult ascertain the overall net effect of these influences* ***due to fundamental differences in the trial populations of ELIANA, ENSIGN and B2101J and Kuhlen et al., and therefore there are high levels of uncertainty.*** The following statement on Page 80 of the report should be amended as follows: '*The second study, Kuhlen et al (2017) provides ~~more complete~~ survival data (n=242) for a period of up to 8 years,* ***with median follow-up of 3.7 years****, on patients recruited to two German paediatric ALL trials and who had relapsed following SCT.* ***However, results should be interpreted with caution as the number of patients at risk after 4 years was very small'****.* The sentences on Page 25–26 and Page 81 (Table 7) should be amended as follows to acknowledge that although there is a difference in prognosis, this is not statistically significant: '*Kuhlen et al. reported a long-term survival rate of 21.5%, however this included T-cell ALL patients who ~~tend to~~ may have a poorer prognosis than B-cell ALL patients* ***(although this difference was numerically but statistically significant)****'.* '*…patients with T-cell ALL tend to have worse prognosis than patients with B-cell ALL as demonstrated by the reported EFS curves*	similarity to the tisagenlecleucel trials, and its generalisability to UK clinical practice: • As acknowledged by the ERG, the proportion of patients with a previous allo-SCT was 100% in Kuhlen versus 54.2% in the tisagenlecleucel trials, hence it has only been conducted in a subset of the population potentially eligible for tisagenlecleucel and the Jeha 2006 study is therefore more inclusive of the overall population. However, 26.3% of patients received a further subsequent SCT. Second SCTs are extremely rare in the UK in this patient population, which raises questions about the representativeness of this study to UK practice. The high rate of SCT is biasing results against tisagenlecleucel as SCT is a curative option and therefore OS in this study is a clear overestimate. • Patients with extramedullary relapse (which are shown to have statistically significantly better outcomes for both OS and EFS) were excluded from the tisagenlecleucel trials, but represent 19.7% of the patient population in the Kuhlen et al. paper.	very substantial limitations and may not be fully reflective of the patient population eligible for tisagenlecleucel. The ERG, however, does note the point raised regarding the extramedullary relapse patients and amends the text accordingly.

therefore it is misleading to state that there is a difference in outcomes between these groups	***(although this difference was not statistically significant)'***.	• Finally, the HR for OS and EFS for T-ALL versus B-ALL (Table II in the Kuhlen study) was also not statistically significant and therefore it is misleading to state that there is a difference in outcomes between these groups. It is important to acknowledge when differences are not significant as this prevents misinterpretations of data. Non-significant data may result from chance rather than an actual observed difference. Taken together, Novartis believe these limitations should be fully acknowledged by the ERG when referring to the Kuhlen paper.	

Section 2: Other comments

Issue 3 Interpretation of the use of tisagenlecleucel in patients with primary refractory disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report, the ERG discuss the use of tisagenlecleucel for primary refractory patients and state that tisagenlecleucel *'would not primarily be used'* in this patient population. The ERG also state that *'Clinical advice to the ERG highlighted that current treatment, such as the NOPHO protocol, has been shown*	Novartis believe that these sentences are not accompanied with appropriate evidence and should be amended as follows: Page 29: *'The ERG is unsure whether primary refractory patients would be treated with tisagenlecleucel-T in practice.~~-~~Clinical advice to the ERG highlighted that current treatment, such as the NOPHO protocol, has been shown to be effective in these patients ~~and thus, tisagenlecleucel-T would not primarily be used~~*[30]'	Primary refractory patients are included in the anticipated licence for tisagenlecleucel and therefore there is no reason to suggest that these patients would not be eligible for tisagenlecleucel in UK clinical practice. In addition, that there are existing effective treatments for patients with primary refractory disease does not preclude the use of tisagenlecleucel	Not a factual error, have changed wording to reflect uncertainty in adoption of the technology in this group.

to be effective in these patients and thus, tisagenlecleucel-T would not primarily be used[30]*'*	Similarly, the following sentence should be removed on Page 36: *'The ERG is unsure whether primary refractory patients would be treated with tisagenlecleucel-T in practice, given that clinical advice to the ERG highlighted that current treatment is effective in these patients,* ***though it should be acknowledged that the existence of effective treatments does not preclude the use of a new therapy***[30]*.'*	in these patients, nor the ability for tisagenlecleucel, as a novel agent, to displace current practice. Novartis therefore feel it would be appropriate for these sentences to amended as such.	

Issue 4 Interpretation of the rate of subsequent SCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG state on Page 15 that *'In addition, the proportion of patients who received an allo-SCT after infusion in all three trials is concerning considering the curative intent of tisagenlecleucel-T.'*	Novartis believe the comments from the ERG here are subjective and may be misinterpreted. The following sentence on Page 15 should be amended as follows: *'In addition, the proportion of patients who received an allo-SCT after infusion in all three trials is concerning considering the curative intent of tisagenlecleucel-T.* ***However, in their response at the clarification questions stage, the company stated that is fully anticipated that tisagenlecleucel will be given with curative intent in UK clinical practice, and feedback from their clinical experts was that the rate of 16.6% of patients receiving a subsequent allo-SCT is an overestimate of likely UK clinical practice****.'*	It is fully anticipated that tisagenlecleucel will be given with curative intent in UK clinical practice. This is also the anticipation of the UK clinical experts consulted as part of this appraisal, who commented that the rate of 16.6% of patients receiving a subsequent allo-SCT is an overestimate of likely UK clinical practice. This rate should be considered in the context of the circumstances at the time of conducting the tisagenlecleucel clinical trials. At the time there were several unknowns regarding the efficacy of tisagenlecleucel and patients were offered the choice to receive a subsequent SCT. Furthermore, initially some physicians in the US chose to consolidate with an allo-SCT following infusion with	Not a factual error. The ERG acknowledge this elsewhere in the report and the committee have access to the PFC responses provided by the company.

		tisagenlecleucel. However, this is no longer considered an appropriate option whilst patients are in remission. If a patient suffers a relapse following tisagenlecleucel infusion, a subsequent allo-SCT is theoretically an option, but UK expert clinician feedback is that the number of people who would be candidates for a subsequent allo-SCT at this stage would be negligible, and now that the efficacy of tisagenlecleucel has been established, clinicians would not use it as a bridge to allo-SCT. Novartis provided the above response at the clarification questions stage and therefore believe the ERG should acknowledge this response alongside their concerns within the report.	

Issue 5 Lack of acknowledgement of limitations in ERG analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG reports throughout that their clinical advisor suggested 10% of patients are cured (or alive at 5 years) whereas our clinical advisors suggested 5% whilst on salvage chemotherapy. However, in the ERG's suggested base case analysis, using the mixture cure modelling approach, the Kuhlen paper estimated cure	The ERG should acknowledge that the cure fractions for salvage chemotherapy predicted in their base case analysis contradict their own clinical expert feedback, that 10% of patients are cured (or alive at 5 years).	The ERG mentions their clinical advisor suggested 10% of patients are cured (or alive at 5 years) whereas our clinical advisors suggested 5% whilst on salvage chemotherapy. Using the mixture cure modelling approach, the Kuhlen paper estimated cure fraction between 13.7 – 16.7% (Page 127). The ERG mentions	Not a factual error, there is significant uncertainty in the effectiveness of salvage chemotherapy and 7.2% is as plausible as 13.7% given ~ 10% cure rate.

fraction was between 13.7 – 16.7% (Page 127). Page 127: *'The cure fractions for OS ranged from 13.7% to 16.6% (Table 22): these are higher than those predicted by Jeha (2006) (the study used by the company in their base-case analysis), but lower than those predicted by Hijiya (2011). The lognormal model was considered the most plausible for EFS and was applied in each of the ERG's scenarios'.*		(Page 20) that the estimated cure fractions from our submission using Jeha 2006 (7.7-9.5%) are consistent with published literature sources and expert advice suggested a 10% cure fraction is reasonable. Given this, the estimated cure fractions of 13.7–16.7% predicted by using the Kuhlen paper are overly-optimistic, and are overestimating the expected cure rate/5-year survival for salvage chemotherapy which, based on clinical opinion (both from the ERG and from Novartis) is between 5–10%.	

Issue 6 Lack of acknowledgement of limitations in ERG analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG's suggested base case analysis results in greater QALYs for salvage chemotherapy ([redacted]) versus blinatumomab ([redacted]).	The ERG should acknowledge that their suggested base case analysis results in clinically implausible QALY predictions for the comparator therapies.	Based on feedback from UK clinical experts, and evidence in the TOWER study of blinatumomab versus salvage chemotherapy (in the adult r/r ALL population), it is highly implausible that salvage chemotherapy is more effective in UK clinical practice than blinatumomab. This should be acknowledged where possible alongside the ERG's base case analysis.	We have edited the text to acknowledge the contradictions, but we do not consider this an indication of the reliability of the Kuhlen data, but rather a product of the substantial uncertainty in the estimates of effectiveness for both salvage chemotherapy and blinatumomab.

Issue 7 Lack of acknowledgement of limitations in ERG analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
A scenario carried out by the ERG considers the costs of only two cycles of blinatumomab based on feedback from clinical experts. Given the efficacy associated with blinatumomab for this scenario continues to be derived from data where patients received five cycles of blinatumomab, the ERG should acknowledge the limitations of this scenario, and include a sentence that highlights that the results should be interpreted with caution.	As such, the ERG should acknowledge the limitations of this scenario and a sentence explaining that the results of this scenario should be interpreted with caution should be included. Page 132 (Table 26): '*The ERG explored a scenario where the duration of treatment of blinatumomab was limited to two cycles' and 'The impact of limiting the number of treatment cycles was a cost saving in the tisagenlecleucel-T arm and the blinatumomab arm of* [redacted] *and* [redacted] *respectively.* ***The results of this scenario should be interpreted with caution given the efficacy of blinatumomab was not altered to reflect patients receiving only two cycles of treatments rather than the five cycles received in von Stackelberg et al. (2016)****'*.	In order for this analysis to be more informative, the efficacy of blinatumomab should be altered to reflect patients receiving only two cycles of treatments rather than the five cycles received in von Stackelberg *et al.* (2016). A sentence explaining the limitations of this suggested scenario should therefore be included. Novartis would also like to note that this scenario is inconsistent with the feedback received from Novartis by four UK clinical experts experienced in the treatment of r/r ALL with blinatumomab, who all stated that they would treat patients with 5 cycles of blinatumomab.	Text edited as suggested

Issue 8 Lack of acknowledgement of limitations in ERG analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 128 of the ERG report states that *'It is therefore likely that many patients will suffer prolonged aplasia, which could persist for the duration of remission.'* Similarly, the exploratory analysis conducted by the ERG that assumes IVIG is received for a	This statement should be amended to include reference to the evidence upon which the statement is based. Furthermore, the statements should acknowledge Novartis's response to the clarification question on this topic where appropriate. *'The 11.4 month duration of IVIG treatment used by the company was derived from a median duration of B-cell aplasia reported in*	Feedback from UK clinical experts consulted in response to this question at the clarification questions stage was that a lifetime duration of IVIG is clinically implausible. Further, their feedback was that the duration of IVIG treatment would typically be aligned with the duration of B-cell aplasia;	Not a factual error –The ERG present this as exploratory analysis for illustrative purposes and is not a statement of fact, this scenario simply uses time to B-cell recovery as suggested by the company's clinical experts.

lifetime is not based on any evidence and has not been appropriately justified by the ERG.	*the ELIANA trial. The use of median duration may be inappropriate for calculating the long-term costs of IVIG use, given that around 70% of patients had not reached B-cell recovery by the latest ELIANA cut-off of 24 months. It is therefore likely that many patients will suffer prolonged aplasia, which could persist for the duration of remission.* ***However, Novartis were able to confirm that feedback from UK clinical experts was that a lifetime duration of IVIG is clinically implausible and UK clinical expert feedback was that the duration of IVIG treatment would typically be aligned with the duration of B-cell aplasia, and therefore the assumption of 11.4 months is reasonable.***'	the estimate of 11.4 months used in the base case of our submission which was based on the time to B-cell recovery, was fully validated by UK clinical experts and is therefore considered the most appropriate here. Without acknowledgement of this response, or the appropriate referencing of this statement based on evidence, Novartis feel these sentences may be taken out of context.	The ERG also highlights that the ERG base-case analysis uses 11.4 months, which is almost certainly too short to represent average cost due to use of the median. The ERG base-case is also far more optimistic than the company's in terms of the proportion of patients receiving IVIG.

Issue 9 Inaccurate reporting of error identified in company model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 119, the ERG reports that *'An error in the company's executable model was identified by the ERG in the company model regarding the application of long-term mortality in the mixture cure models. In the company's model, mortality in each period was estimated as the higher of that predicted by the mixture cure model and (sex and age adjusted) general population mortality with a SMR applied. This mortality rate was then applied to the proportion of*	Reference to this approach as an error is factually inaccurate, as this approach was intentional from Novartis. Furthermore, Novartis do not consider the ERG's approach here to be appropriate (see justification for amendment) and therefore suggest the ERG remove this change from their analysis.	Reference to this approach as an error is factually inaccurate, as this approach was intentional from Novartis. We believe this is the most valid approach as the cured fraction should follow general mortality, and the non-cured fraction would die quickly and they should not therefore follow either general mortality or SMR-adjusted mortality. The SMR-adjusted general population mortality was intended to represent the mortality rate for long-term (post-5 year) survivors in the non-mixture cure	The ERG consider the approach used by the company to be incorrect, and had assumed that this was not intentional as it produces implausible results when alternative SMRs are applied (dead patients can return to life in subsequent periods of the model). As such, the ERG stands by the correction made and therefore does not make any amendments to the report or model. The ERG, however, recognises that the company

patients estimated to be alive according to the mixture cure modelling. This meant that when the modelled OS could not deviate from the curve estimated by the mixture cure model even when general population mortality based values were being used.'		approach, when there is no distinction in the modelled population between 'cured' and 'non-cured' individuals. However, in the mixture cure model approach, the population is assumed to consist of a 'cured' and 'uncured' cohort. General population mortality is applied to the 'cured' cohort, and it is assumed that this applies for the remainder of their lifetime, hence it is not necessary to apply any other mortality rate. For the 'uncured' population, it was assumed that the most relevant survival curve was the extrapolated curve from the mixture cure analysis, not the SMR-adjusted general population mortality rate, as these individuals were not expected to be long-term survivors. In addition, it can be seen in the mixture cure model that the OS curve has almost reached the cure fraction after 61 months, and hence it is reasonable to assume that the remaining patients alive are the 'cured' fraction of the population.	considers their original approach to be the most appropriate and have highlighted this issue to NICE so that can be fully considered by the committee.

Issue 10 Lack of reference to clinical expert opinion acknowledgement where appropriate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On several pages in the ERG report, the ERG refer to the trial populations of the three tisagenlecleucel trials being '*restricted to patients with a life*	The following sentences should be amended to acknowledge the clinical expert feedback: *'The clinical evidence is also restricted to patients with a life expectancy of 12 weeks or more. The ERG considers that this may result in patients*	Where appropriate, the clinical expert feedback should be acknowledged each time the ERG refer to the life expectancy restriction of the trials otherwise	Not a factual error

expectancy of 12 weeks or more… which may result in patients selected onto these trials being generally fitter and healthier than the eligible patient population', e.g. on Page 12, Page 14, Page 30, Page 36, and Page 57. However, on Page 30 of the ERG report, the ERG acknowledge that '*Clinical advice to the ERG is that although this might exclude some of the eligible patient population, in practice, patients who are extremely ill would be treated with standard chemotherapy-based salvage treatment rather than tisagenlecleucel-T. Also, as there is a delay of several weeks between being assigned tisagenlecleucel-T and receiving infusion, restricting tisagenlecleucel-T to patients likely to survive this waiting period is reasonable.'*	*selected onto these trials being generally fitter and healthier than the eligible patient population.* ***However, clinical advice to the ERG is that although this might exclude some of the eligible patient population, in practice, patients who are extremely ill would be treated with standard chemotherapy-based salvage treatment rather than tisagenlecleucel-T. Also, as there is a delay of several weeks between being assigned tisagenlecleucel-T and receiving infusion, restricting tisagenlecleucel-T to patients likely to survive this waiting period is reasonable.'*** The same additional text should be added to the similar statements that are made on Page 12, Page 14, Page 30, Page 36, and Page 57.	these sentences may be taken out of context.	

Issue 11 Lack of acknowledgement of statements relating to newly diagnosed ALL

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 of the ERG report states *'Long-term survival rates for B-cell ALL patients are reported to be 40% to 50%.*[5, 6]' Further on Page 29, the ERG report states that *'The incidence*	These sentences highlighted on Pages 25 and 29 should be amended to make it clear that these figures are referring to the ALL population as a whole, and newly diagnosed ALL, rather than the population eligible for tisagenlecleucel. (relapsed/refractory ALL).	These sentences may be taken out of context if they are not amended to clarify that they are not referring to the population eligible for tisagenlecleucel (and instead referring to the ALL population as a whole, and newly diagnosed ALL).	Edited both sections highlighted by the company to emphasise this.

of ALL among children aged 2 to 3 years old is approximately fourfold to fivefold greater than that for children aged 10 years and older[31]. Therefore, the trial populations do not fully reflect the characteristics of the eligible NHS population.' The above statements refer to the ALL population as a whole, and newly diagnosed ALL, rather than the population of interest.			

Issue 12 Lack of acknowledgement of the use of adult rather than paediatric data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The report makes misleading assumptions regarding the effectiveness of blinatumomab in paediatric patients based on data in the adults population. Page 79 of the ERG report states that: *'… assuming similar relative effectiveness in a paediatric population we would expect to see significant overlap in the KM curves for FLA-IDA and blinatumomab. This would rule out the selected Jeha et al along with a number of the other studies identified and would potentially favour the Hijiya et al (2011) study.'*	The following statement on Page 79 of the report should be amended as follows: '*Evidence from on the relative effectiveness of* ***salvage*** *chemotherapy ~~(FLAG-IDA, which is used adults with ALL~~) and blinatumomab in the TOWER trial suggests that the long-term benefits of blinatumomab over salvage chemotherapy are relatively small* ***in the adult ALL population*** *(****Error! Reference source not found.****). ~~and~~ Assuming similar relative effectiveness in a paediatric population (****an assumption which is associated with high levels of uncertainty****) we ~~would~~ might expect to see significant overlap in the KM curves for FLA-IDA and blinatumomab. This ~~would~~* ***may*** *rule out the selected Jeha et al along with a number of the other studies identified and would potentially favour the Hijiya et al (2011) study.* ***However, it is very difficult, and somewhat implausible to make***	It is important to explicitly state whether data are derived from adult or paediatric populations as outcomes can vary and can not automatically be considered comparable.	Not a factual error, it is acknowledged several times in the ERG report that TOWER is in adults whose outcomes are generally worse.

	***assumptions on the outcomes achieved in paediatric patients with ALL when referring to data derived from adults, particularly as FLAG-IDA (and several other chemotherapy regimens) rather than FLA-IDA alone was investigated in this case**.'*		

Issue 13 Misreporting following error in NICE final scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 14 of the ERG report, the ERG refer to the NICE scope, stating that the relevant comparators should be *'Established clinical management … at one of the following lines of therapy … any bone marrow relapse, within 6 months or less, after allogenic SCT'.*	As highlighted in our company submission, this was an error in the NICE final scope and this wording should be amended to the following: *'Established clinical management … at one of the following lines of therapy: … any bone marrow relapse, ~~within 6 months or less~~* ***within 4 months or more*** *after allogenic SCT'* The same amendment should also be made on Page 30.	The draft SmPC for tisagenlecleucel states that it is not recommended for patients to receive tisagenlecleucel within 4 months of undergoing an allo-SCT, and therefore this sentence should be amended as such.	Correction to the effect of the company's suggestions made.

Issue 14 Lack of acknowledgement of clarification questions response

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 21, the ERG report states that *'Particular consideration should be given to additional infrastructure requirements that have not been captured in the presented analyses. The ERG highlight particular uncertainty surrounding additional paediatric ICU capacity which may need to be made*	As Novartis responded to these queries at the clarification questions stage, Novartis believe the following statements should be amended to acknowledge our response, as appropriate. The sentence on Page 21 should be amended as follows: *'Particular consideration should be given to additional infrastructure requirements that have not been captured in the presented analyses. The ERG highlight particular*	In the response to the clarification questions, Novartis stated that the only additional requirements for the administration of tisagenlecleucel will be training on the Novartis ordering system and the safety training as required by EMA (which will be provided by Novartis). As such, this training will require attendance from prescribing	Not a factual error

available (even if not used) to ensure that patients receiving tisagenlecleucel-T can be guaranteed access to appropriate services if and when required, without adversely affecting the provision of care to other patients.' Further on Page 117, the ERG report states: *'Given the complexity of this intervention and patient care needs, the lack of a clear service specification for the production, provision, and administration of tisagenlecleucel-T on the NHS, the ERG considers that there are important remaining uncertainties regarding the quantification of additional resource and investment requirements for the NHS.'*	*uncertainty surrounding additional paediatric ICU capacity which may need to be made available (even if not used) to ensure that patients receiving tisagenlecleucel-T can be guaranteed access to appropriate services if and when required, without adversely affecting the provision of care to other patients.* ***However, in response to this question at the clarification questions stage, Novartis stated that the only additional requirements for the administration of tisagenlecleucel will be training on the Novartis ordering system and the safety training as required by EMA (which will be provided by Novartis). It is not anticipated that ICU beds will need to be routinely reserved and therefore, beyond the training time, there are no further resource/cost implications anticipated by Novartis that have not been considered.'*** The same amendment should also be made on Page 117.	clinicians, nurses and ICU staff, the cost of which had not been included within the base case analysis. It is not anticipated that ICU beds will need to be routinely reserved and therefore, beyond the training time, there are no further resource/cost implications anticipated by Novartis that have not been considered.' By not acknowledging Novartis' response to this question in the ERG report, these statements may be misinterpreted.	

Issue 15 Lack of acknowledgement of clarification questions response

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report, the ERG refer to the manufacturing time of tisagenlecleucel, e.g. on Page 12: *'The company state the complete process takes 3 weeks. However, the process took 16 weeks in the ELIANA trial, which has considerable implication for eligible patients due to the pace of disease progression and their*	The following sentence on Page 12 should be amended to acknowledge the response to the relevant clarification question*: 'The company state the complete process takes 3 weeks. However, the process took 16 weeks in the ELIANA trial.~~, which has considerable implication for eligible patients due to the pace of disease progression and their estimated life expectancy of 3-9 months.~~* ***The ERG requested clarification for this difference at***	The ERG should acknowledge the explanation provided by Novartis in response to this matter at the clarification questions stage, that included further published evidence of the real-world manufacturing time in clinical practice. Without this acknowledgement, Novartis feel	Not a factual error – the company's explanation was provided in the ERG report.

estimated life expectancy of 3-9 months.' Similar statements are made on Page 14, Page 57, and Page 142: However, an explanation for the difference between the manufacturing time reported in the ELIANA trial and the anticipated manufacturing time in current clinical practice was requested at the ERG clarification questions stage to which Novartis provided published evidence of the real-world manufacturing time in clinical practice. This information should therefore be provided alongside the ERG's comment in relation to manufacturing time here, and elsewhere throughout the document.	***the clarification questions stage, to which Novartis provided the explanation that recent data have been published on the throughput time for a total of 37 commercial patient orders (for B-ALL) that were placed for tisagenlecleucel.[5] Median throughput time for the 37 commercial batches from receipt of leukapheresis material and required documentation at the manufacturing facility to return of tisagenlecleucel product to treatment site was 23 days (range, 21–37 days). For the batch with the 37-day throughput time, a laboratory error in the quality control part of testing and disposition was detected, which prevented timely release of the manufactured batch.[5]*** ***These published data correspond to the prespecified manufacturing time of 3–4 weeks in the SmPC and quoted in the submission, and ongoing refinements are expected to further decrease the throughput time from receipt of leukapheresis material to return of manufactured product to 21 days.'*** The same additional text should be added to the similar statements that are made on Page 12, Page 14, Page 30, Page 57, and Page 142.	these sentences may be taken out of context.	

Issue 16 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of the ERG report states that *'The CS considered the relevant comparators to be*	The following sentence on Page 13 should be amended as follows: *'The CS considered ~~the relevant comparators to be salvage~~*	Misreporting of statements from the company submission.	Text corrected to "The CS considered salvage chemotherapy (FLA-IDA) and

salvage chemotherapy, specifically FLA-IDA for paediatric patients and FLAG-IDA for TYA patients or blinatumomab'. This is incorrect given the company submission does not mention FLAG-IDA as a relevant comparator. This is because feedback from four UK clinical experts experienced in the treatment of both paediatric and young adult patients with r/r ALL stated that if they were to use salvage chemotherapy they would use the FLA-IDA regimen only. When asked if they would use FLAG-IDA, the clinicians responded that they would not, hence this regimen was not included as a relevant comparator within the submission.	~~*chemotherapy, specifically FLA-IDA for paediatric patients and FLAG-IDA for TYA patients or blinatumomab*~~ ***salvage chemotherapy (FLA-IDA) and blinatumomab to represent the most relevant comparators to tisagenlecleucel within the treatment pathway for paediatric and young adult patients who have r/r B-cell ALL****'.*		blinatumomab to represent the most relevant comparators to tisagenlecleucel for paediatric and young adult patients with r/r B-cell ALL."

Issue 17 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15 of the ERG report states that *'There was no evidence presented to justify using clofarabine as a proxy for FLA-IDA.'* This statement is factually inaccurate, given that throughout the company submission Novartis state that no data were identified for FLA-IDA and therefore	The following statement on Page 15 should be removed or reworded as follows: '~~*There was no evidence presented to justify using clofarabine as a proxy for FLA-IDA*~~ ***In the absence of any identified data for FLA-IDA, the company sought UK expert clinical feedback to justify the use of Jeha 2006 as a proxy for FLA-IDA'.***	Misreporting of statements from the company submission.	Reworded: 'There was **insufficient** evidence presented to justify using clofarabine as a proxy for FLA-IDA"

feedback from UK clinical experts experienced in the treatment of ALL was used to justify this approach. This statement should therefore be removed or reworded accordingly.			

Issue 18 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 16 of the ERG report it states that '*Cost-effectiveness was assessed over a lifetime time horizon of 88 years with a 3.5% discount rate applied to both costs and QALYs. No other rates were explored in the CS*'. This in inaccurate as discount rates of 1.5% and 6% were both explored in scenario analyses.	It is proposed that the second sentence is removed here so that the ERG report on Page 16 reads only that '*Cost-effectiveness was assessed over a lifetime time horizon of 88 years with a 3.5% discount rate applied to both costs and QALYs. ~~No other rates were explored in the CS.~~*'	Misreporting of statements from the company submission.	Corrected

Issue 19 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 18 of the ERG report, it states that '*the deterministic base case ICER was £25,404 per QALY, and the mean probabilistic ICER was £25,404 per QALY*'. The value of £25,404 in the final sentence has been misreported as the value should be £27,066.	This statement in the ERG report on Page 18 should read: '*The deterministic base case ICER was £25,404 per QALY, and the mean probabilistic ICER was **£27,066** per QALY*'.	Misreporting of ICERs from the company submission.	Corrected

Issue 20 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The cure fraction estimates for blinatumomab have been misreported. Page 18: '*The ERG questions the application of a cure model to blinatumomab, and again notes the uncertainty in cure fraction estimates (2.9 – 21.7%)*'. Page 115: *'…again indicated by the uncertainty in cure fraction estimates (2.9 – 21.7%).'*	These sentences in the ERG report on Page 18 and Page 115 should instead read: '*The ERG questions the application of a cure model to blinatumomab, and again notes the uncertainty in cure fraction estimates (**3.9** – 21.7%).*' *'…again indicated by the uncertainty in cure fraction estimates (**3.9** – 21.7%).'*	Misreporting of data from the company submission.	Corrected

Issue 21 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The cure fraction estimates for salvage chemotherapy have been misreported. Page 19: *'While cure models were discarded by the company on the grounds of clinical plausibility, the ERG highlights that the estimated cure fractions (7.7 – 9.5%) are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable.'* Page 86: *'…suggesting that the predicted proportion of patients alive at 5 years based on the best statistically fitting mixture cure*	These sentences in the ERG report on Page 19, Page 86 and Page 115 should read as follows, as these are the cure fraction estimates from the top 3 best-fitting mixture cure models for salvage chemotherapy: '*While cure models were discarded by the company on the grounds of clinical plausibility, the ERG highlights that the estimated cure fractions (**7.2** – **9.4**%) are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable.*' '*…suggesting that the predicted proportion of patients alive at 5 years based on the best statistically fitting mixture cure models was too high (range **7.2%** to **9.4%**).'*	Misreporting of data from the company submission.	Corrected

models was too high (range 7.7% to 9.5%).' Page 115: *'…the ERG highlights that these estimated cure fractions (7.7 – 9.5%) are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable…'*	*'…the ERG highlights that these estimated cure fractions (**7.2 – 9.4%)** are consistent with published literature sources and expert advice suggesting a 10% cure fraction is reasonable…'*		

Issue 22 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Median survival for the pooled tisagenlecleucel population has been misreported. Page 19*: '…the pooled median survival is 46 months'.*	This statement in the ERG report on Page 19 should read, '…*the pooled median survival is* [redacted]*.*' This should also be marked as Academic in Confidence as this data is unpublished.	Misreporting of data from the company submission.	Corrected

Issue 23 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The proportion of patients who had relapsed within 6 months in von Stackelberg *et al.* (2016) has been misreported. Page 52: *'…the cohort had particularly unfavourable characteristics as 70% of patients had relapsed within 6 months of the previous treatment attempt'*.	This sentence in the ERG report on Page 52 should read, *'…the cohort had particularly unfavourable characteristics as **71%** of patients had relapsed within 6 months of the previous treatment attempt'*.	Misreporting of data from the company submission.	Corrected

Issue 24 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The threshold for reporting AEs for the Jeha *et al.* (2006) trial has been misreported. Page 89: *'…Grade 3 or higher AEs occurring in ≥5% of subjects in the Jeha study were used to estimate AE rates for FLA-IDA'*. Page 89: '*AEs grade 3-4 occurring in 5% or more of subjects…*'.	These sentences of the ERG report on Page 89 should read, *'…Grade 3 or higher AEs occurring in **≥10%** of subjects in the Jeha study were used to estimate AE rates for FLA-IDA' and 'AEs grade 3-4 occurring in **10%** or more of subjects…*'.	Misreporting of data from the company submission.	The first instance referred to by the company is found in Table 4, Page 65, and has been corrected. The second instance has been corrected using the company's suggested text.

Issue 25 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The standard error of mean utility values is misreported in Table 8 of the ERG report on Page 92: '*Progressive Disease for Kelly et al. 0.75 (0.16)'* '*Event-free survival for Kelly et al. 0.91 (0.02)*' '*Long-term survival for Kelly et al. 0.91 (0.02)*'	These statements in the ERG report on Page 92 should read: '*Progressive Disease for Kelly et al. 0.75 (**0.02**)',* *'Event-free survival for Kelly et al. 0.91 (**0.16**)'* *'Long-term survival for Kelly et al. 0.91 (**0.16**)*'	Misreporting of data from the company submission.	The standard error values quoted in the ERG report reflect those used in the company's economic model, and those described in the table of PSA inputs found in the main company submission (Table 63). They also appear to reflect Kelly *et al*. The ERG suggests Table 43 in the CS quotes incorrect values, as they do not reflect those in the economic model. This represents an error in the company's model if not the case.

Issue 26 Misreporting from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The absolute incremental QALY gain for tisagenlecleucel vs blinatumomab is misreported in Table 16 of the ERG report on Page 106: '*Abs. inc. vs blinatumomab:* [redacted], [redacted], [redacted], [redacted], [redacted]'.	These values in Table 16 on Page 106 should read '[redacted], [redacted], [redacted], [redacted], [redacted]', respectively.	Misreporting of data from the company submission.	Corrected

Section 3: Confidentiality highlighting amendments

Issue 27 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required in the following sentence on Page 13: '*ENSIGN is a study of* [redacted] *patients*.' and '*The full ITT population comprised* [redacted] *patients*' on Page 13.	Academic in Confidence highlighting can be removed from these sentences as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 28 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 18: *'…alternative mixture cure models for OS (between* [redacted] *to* [redacted]*),'* on Page 18.	The following cure fraction estimates should be highlighted as Academic in Confidence: [redacted]' and [redacted]'	These figures are not published and should thus be marked as Academic in Confidence.	Corrected

Issue 29 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required in the following sentence on Page 38: '*…open-label study that is evaluating tisagenlecleucel-T in* [redacted] *patients'* and '*The full ITT population, which includes all enrolled patients, comprised* [redacted] *patients'* on Page 38.	Academic in Confidence highlighting can be removed from these sentences as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 30 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 40: '*Approximately* [redacted] *are event-free at 12 months, and* [redacted] *are alive at 12 months*' on Page 40.	The following figures should be highlighted as Academic in Confidence: '[redacted]' and '[redacted]'	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected

Issue 31 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 40: '*Approximately [redacted] are event-free at 12 months, and [redacted] are alive at 12 months'* on Page 40.	The following figures should be highlighted as Academic in Confidence: '[redacted]' and '[redacted]'	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected

Issue 32 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 75: *'…with [redacted] of patients receiving more than one dose of tisagenlecleucel-T. Furthermore, [redacted] of patients received…*', '*uncertainty surrounding the number ([redacted]) of patients who did not require bridging therapy;…*' and '*…patients aged 18-25, who made up [redacted] of the…*' on Page 75.	The following figures should be highlighted as Academic in Confidence: '[redacted]', '[redacted]', '[redacted]' and '[redacted]'	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected

Issue 33 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 76: *'…patients with two or more relapses (comprising [redacted] of the B2101J population;…'* on Page 76.	The following figure should be highlighted as Academic in Confidence: '[redacted]'	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected

Issue 34 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for Figure 22 on Page 77 (Kaplan-Meier and parametric extrapolations of overall survival for tisagenlecleucel-T).	This figure should be marked as Academic in Confidence.	This figure was marked as confidential in the Company Submission but this has not been transferred over to the ERG report.	Corrected

Issue 35 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 82: '*…the estimated cure fraction was [redacted] The company noted that this rate is consistent with the pooled*	The following figures should be highlighted as Academic in Confidence: '[redacted]', '[redacted]' and '[redacted]'	These figures are not published and should thus be marked as Academic in Confidence.	Corrected

tisagenlecleucel-T clinical trial data, which provides follow-up to almost five years ([redacted]), at which point [redacted] of patients remain alive' on Page 82.			

Issue 36 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 83: *'…between 13.1 months follow up in ELIANA (December 31st 2017 data cut-off date) and [redacted] months in B2101J…*', *'…predicted cure fraction reported across the alternative mixture cure models for OS (between [redacted] to [redacted])…*' and '*predicted cure fraction exceeds the observed number of EFS events from the three tisagenlecleucel-T trials of [redacted]*' on Page 83.	The following figures should be highlighted as Academic in Confidence: '[redacted]', '[redacted]', '[redacted]' and '[redacted]'	These figures have not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 37 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 87:	The following unpublished data should be highlighted as Academic in Confidence:	This figure has not been published and should thus be marked as Academic in Confidence.	Corrected

'*The estimated 2 to 5 year mortality rate using the company's base case assumptions are far in excess of that observed for other therapies considered; respectively* [redacted] *and 62% of tisagenlecleucel-T and blinatumomab patients alive at 2 years are alive at 5 years...*' on Page 87.	'[redacted]'		

Issue 38 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 88: *'…the estimated cure fractions of* [redacted] *and* [redacted] *produced by the Weibull, and log-logistic respectively were inconsistent with the cure fraction predicted by the OS models of* [redacted]' and '*the generalised gamma curve, which estimated the cure fraction as* [redacted]' on Page 88.	The following figures should be highlighted as Academic in Confidence: '[redacted]', '[redacted]', '[redacted]' and '[redacted]'	These figures have not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 39 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 89: '*This is demonstrated by the wide range of cure fractions predicted by the model ([redacted] to [redacted])*' on Page 89.	The following figures should be highlighted as Academic in Confidence: '[redacted]' and '[redacted]'	These figures have not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 40 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 116: '*The cure fraction estimates generated using mixture cure models for tisagenlecleucel-T varied between [redacted] and [redacted]...*' and '*The company's base case used the second most optimistic cure fraction of [redacted], in excess of the observed proportion in long-term EFS of [redacted]...*' on Page 116.	The following unpublished data should be highlighted as Academic in Confidence: '[redacted]', '[redacted]', '[redacted]' and '[redacted]'	These figures have not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 41 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 119: '*KM data on time on time to B-cell recovery remain incomplete and approximately [redacted] of patients who achieved CR were yet to achieve B-cell recovery…*' on Page 119.	This figure should be highlighted as Academic in Confidence: '[redacted]'	This figure has not been published and should thus be marked as Academic in Confidence.	Corrected – also corrected typo 'on time on time'.

Issue 42 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 122: '*The ERG noted that none of the [redacted] patients who did not receive infusion…' and 'with [redacted] of those alive in the first month (half-cycle distribution) incurring bridging chemotherapy and [redacted] receiving lymphodepleting chemotherapy…*' on Page 122.	The following unpublished data should be highlighted as Academic in Confidence: '[redacted]', '[redacted]' and '[redacted]'	Data presented have not yet been published and should thus be marked as Academic in Confidence.	Corrected

Issue 43 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required for the following sentence on Page 133. '*…the mean time to CRS, based on data extracted from ELIANA, ENSIGN and B2101J trials, and was estimated as* [redacted] *…*' on Page 133.	The following unpublished data should be highlighted as Academic in Confidence rather than Commercial in Confidence: '[redacted]'	This figure has not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 44 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 138. '*This predicts a cure-fraction of* [redacted] *compared to* [redacted] *in the company's base and* [redacted] *in the ERG's base-case*' on Page 138.	The following unpublished data should be highlighted as Academic in Confidence: '[redacted]', '[redacted]' and '[redacted]'	These figures have not been published and should thus be marked as Academic in Confidence.	Corrected

Issue 45 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is required in the following sentence on Page 142:	The following unpublished data should be highlighted as Academic in Confidence: '[redacted]', '[redacted]' and '[redacted]'	These data have not yet been published and should thus be	Corrected

'*…with a pooled median OS of [redacted]. Comparisons with trials of blinatumomab and clofarabine suggested a strong benefit of tisagenlecleucel-T with hazard ratios of [redacted] when compared to blinatumomab and [redacted] with clofarabine*' on Page 142.		marked as Academic in Confidence.	

Issue 46 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Some of the Academic in Confidence highlighting is no longer required in Table 2 on Page 38.	Some of the Academic in Confidence highlighting can be removed for data on ORR and OS from ENSIGN as this information is now in the public domain. **Please refer to the Appendix for a copy of Table 2 from the ERG report with updated highlighting. (A footnote was also missing from this table which has now been added.)**	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 47 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 57: '*The full ITT populations for ELIANA, ENSIGN and B2101J*	The Academic in Confidence highlighting can be removed for ENSIGN ('[redacted] *patients*') as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

were [redacted] patients, [redacted] patients and [redacted] patients' on Page 57.			

Issue 48 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 37 and Page 57: '*The median time between enrolment and infusion of tisagenlecleucel-T in ELIANA, ENSIGN and B2101J was [redacted] days, [redacted] days and [redacted] days.*' on Page 37 and Page 57.	The Academic in Confidence highlighting can be removed for ENSIGN ('[redacted] *days*') as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 49 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 44: '*…at the latest data cut-off (median follow up [redacted] months)'* and '*A median follow-up of [redacted] months is inadequate…*' on Page 44.	This Academic in Confidence highlighting can be removed as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 50 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 36: '*The median age in the full ITT population of ENSIGN is higher than in the infused-only population in ([redacted] years vs [redacted] years, respectively)*' on Page 36.	Academic in Confidence highlighting can be removed from '[redacted] *years*' as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 51 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 39. '*…the 'full analysis' set (n=[redacted]) and the efficacy analysis set (n=[redacted]).*' on Page 39.	This Academic in Confidence highlighting can be removed as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 52 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required for the following sentence on Page 44: '*…of 42 patients, the ORR was [redacted], including [redacted] with CR, at the latest data cut-off (median follow up [redacted] months). Of the patients who achieved an overall remission rate of CR or CRi, [redacted] of patients…*' and '*There were [redacted] patients enrolled in the trial who did not receive tisagenlecleucel-T*' on Page 44.	This Academic in Confidence highlighting can be removed as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 53 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required in the following sentence on Page 141: '*The median OS for tisagenlecleucel-T was reported as* [redacted]*…*' on Page 141.	This Academic in Confidence highlighting can be removed as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Issue 54 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Academic in Confidence highlighting is no longer required in the following sentence on Page 50: '*Serious adverse events (SAE) were reported in* [redacted]*,* [redacted] *and* [redacted] *of patients in the ELIANA, ENSIGN and B2101J trials, respectively*' on Page 50.	This Academic in Confidence highlighting can be removed for ENSIGN ('[redacted]') as this information is now in the public domain.	Revisions have been made to confidentiality highlighting following publication of data from ENSIGN.	Corrected

Appendix

Table 2 (Page 38 of ERG report)

	ELIANA (N=79) (N=77 for ORR)	**ENSIGN (N=58) (N=42 for ORR)**	**B2101J (N=56)**
ORR (CR+CRi) (95% CI; p value)	[redacted]	29 (69.0) (52.9, 82.4; <0.0001*)	[redacted]
EFS			
% event free at 6 months (95% CI)	[redacted]	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]	[redacted]
OS			
% at 6 months (95% CI)	[redacted]	79.3 (64.9, 88.4)	[redacted]
% at 12 months (95% CI)	[redacted]	62.6 (45.8, 75.6)	[redacted]
Median (months) (95% CI)	[redacted]	23.8 (8.8, NE)	[redacted]

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical engagement document for clinical, patient and commissioning experts and Novartis comment

Tisagenlecleucel-T for treating relapsed or refractory diffuse B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]

1.1. This document has been prepared by the NICE technical team.

1.2. NICE would like to engage with the company, clinical, patient and commissioning experts to comment on key areas of uncertainty in this appraisal.

The responses will be used by the technical team to inform the Appraisal Committee in preparation for the appraisal committee meeting on 22 August 2018.

1.3. This document includes questions on key areas of uncertainty for your feedback and comment. This document is based on the key evidence and views submitted by the company, nominated clinical and patient experts and the ERG.

Questions for your comment: tisagenlecleucel-T for relapsed or refractory B-cell ALL [ID1167]

Question 1: What population are likely to receive tisagenlecleucel-T for relapsed or refractory B-cell ALL in clinical practice?	
Questions for engagement	• *Is tisagenlecleucel likely to be used for people with Philadelphia positive disease?* • *Are the results for Philadelphia negative disease generalisable to those with Philadelphia positive disease*?
Why this issue is important	NICE appraises a technology within its marketing authorisation. The CHMP positive opinion for tisagenlecleucel -T covers both Philadelphia negative and positive B-cell ALL. However, the company does not present any clinical or cost effectiveness evidence for the B-cell Philadelphia positive population within its submission
Background/ description of issue	The CHMP positive opinion for tisagenlecleucel-T states that it is indicated for 'the treatment of paediatric and young adult patients (up to 25 years of age) with B-cell ALL that is refractory or in second or later relapse'. The company states that the proportion of patients with Philadelphia positive ALL within the eligible patient population will constitute a small minority (<3%). It also stated that there is also a distinct lack of data in the Philadelphia positive ALL population, for both tisagenlecleucel-T and the relevant comparators in this indication, and therefore it was not feasible for it to present a robust comparison for this subgroup and as such, no comparison has been presented within its clinical and cost-effectiveness submission.

Question 2: What is the treatment pathway for people younger than 18 years of age with primary refractory B-cell ALL?	
Questions for engagement	• *Do people younger than 18 years of age with primary refractory B-cell ALL routinely receive treatment based on the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol?* • *Is the company's position of tisagenlecleucel-T in the treatment pathway for people younger than 18 years of age with primary refractory disease appropriate?*

Why this issue is important	The company has positioned tisagenlecleucel-T as a first line treatment for primary refractory disease and identified FLA-IDA and blinatumomab as the appropriate comparators. However, there is no analyses provided to account for the NOPHO protocol which suggests that tisagenlecleucel-T would be used later in the treatment pathway.
Background/ description of issue	The company submission does not include the NOPHO protocol treatment option for patients under the age of 18 years with primary refractory ALL. The ERG stated that the NOPHO protocol treats patients based on risk-group stratification for remission induction therapy, and that the protocol has shown substantial improvements in survival for these patients. Patients aged 18 years and older are not typically treated with the NOPHO protocol; rather that they tend to receive blinatumomab. However, there are no specific guidelines for these patients. The ERG also stated that as the NOPHO protocol for people under the age of 18 years with primary refractory disease is highly effective, these patients would be less likely to receive tisagenlecleucel-T. Rather, tisagenlecleucel-T would be used as treatment for patients further along the treatment pathway.

Question 3: What is the current treatment pathway for people with B-cell ALL with 2 or more disease relapses?	
Questions for engagement	• *Where is blinatumomab used in the current treatment pathway for Philadelphia negative disease* o *For people younger than 18 years of age?* o *For people aged 18-25 years?* • *Is blinatumomab an appropriate comparator to tisagenlecleucel-T for relapsed disease?* o *For people younger than 18 years of age?* o *For people aged 18-25 years*?
Why this issue is important	Both the company and the clinical advisor to the ERG state that blinatumomab would not typically be given to patients in second or later relapse because it is being used earlier in the treatment pathway. This raises

	concerns regarding the generalisability of the results from the tisagenlecleucel-T clinical trials to the population for whom tisagenlecleucel-T will be used in clinical practice England and the validity of blinatumomab as a comparator to tisagenlecleucel-T.
Background/ description of issue	1. NICE guidance is already in place for the ~8.3% of patients aged 18 years or older, who would typically receive blinatumomab as a first-line salvage therapy. This means this population would not be eligible for blinatumomab again after a second relapse, as considered in this appraisal. Clinical advice to the ERG and company suggests this is increasingly becoming the case in paediatric patients; as blinatumomab is used earlier in the treatment pathway in the NHS. 2. The ERG also considers the impact of blinatumomab use earlier in the treatment pathway to raise the issue of eligibility for tisagenlecleucel-T after 2 or more relapses. A key exclusion criterion of the 3 tisagenlecleucel-T trials was the previous use of an anti-CD19 therapy such as blinatumomab, because of the hypothetical impact upon treatment efficacy and the chance of CD19-negative relapse, which was observed in 22% of tested relapses in the paediatric blinatumomab trial. This casts some uncertainty upon the relevance of the trial data, as the efficacy of tisagenlecleucel-T has not been demonstrated in patients previously treated with an anti-CD19 therapy. The ERG considers that CD19 expression would need to be quantified before patients could be considered for treatment with tisagenlecleucel-T, as patients with weak or no expression of CD19 would gain little to no benefit from this treatment. Both the company and the clinical advisor to the ERG state that blinatumomab would not typically be given to patients in second or later relapse because it is being used earlier in the treatment pathway. This raises uncertainty regarding the validity of blinatumomab as a comparator to tisagenlecleucel-T. 3. The ERG noted that blinatumomab has never been appraised in a paediatric population for this indication. The trial results suggest lower efficacy of blinatumomab in children than in adults.

Question 4: Is it appropriate to use clofarabine as a proxy for the efficacy of FLA-IDA (that is salvage chemotherapy)?	
Questions for engagement	• *Is clofarabine used in clinical practice in the NHS in England?* • *Is there any evidence to support the equivalence of FLA-IDA and clofarabine?*
Why this issue is important	Both the company and the ERG consider FLA-IDA to be a relevant comparator to tIsagenlecleucel-T. However there is a lack of data on FLA-IDA.
Background/ description of issue	The company excluded clofarabine as a comparator because of its toxicity level and hence its rare use in the NHS in England UK. Clinical advice to the ERG agreed that clofarabine is not a suitable comparator. However, as a result of the lack of data on FLA-IDA, the company uses clofarabine monotherapy efficacy data as a proxy for FLA-IDA. The ERG is uncertain about the validity of this proxy given that clofarabine is rarely used in clinical practice and there are concerns regarding its toxicity.

Question 5: Other areas of uncertainty	
Long term usage and costs of IVIG treatment - real world experience	• *Would people younger than 18 years of age require continued IVIG treatment and for how long?* • *Would people aged 18-25 years require continued IVIG treatment and for how long?*

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August 2018

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
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- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 22 August 2018

Deadline for comments **12pm Monday 13 August 2018** email: **tacommc@nice.org.uk /NICE DOCS**

About you

Your name	[redacted]
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals Ltd
Are you (please tick all that apply)	☒ a representative from the company (Novartis)? ☐ a clinical expert? ☐ a commissioning expert? ☐ a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Questions for engagement

Question 1: What population are likely to receive tisagenlecleucel-T for relapsed or refractory B-cell ALL in clinical practice?	
Is tisagenlecleucel likely to be used for people with Philadelphia positive disease?	Patients with Philadelphia chromosome-positive ALL were eligible for inclusion in the tisagenlecleucel trials if they had failed or were intolerant to two lines of tyrosine kinase inhibitor (TKI) therapy, or were contraindicated for TKI therapy. These patients are also included within the anticipated licence for tisagenlecleucel (the licence does not stipulate either Philadelphia chromosome-positive or Philadelphia chromosome-negative disease). There is no reason to suggest that tisagenlecleucel should not be used in these patients in UK clinical practice. It should be noted that the number of patients with Philadelphia chromosome-positive ALL in this setting that would be eligible for tisagenlecleucel is extremely small, and is anticipated to be only

	one or two patients per year in England. For these patients, treatment options are severely limited, and prognosis is extremely poor. The inclusion of these patients within the tisagenlecleucel trials and within the tisagenlecleucel licence therefore offers these patients a possible treatment option and the hope for a cure.
Are the results for Philadelphia negative disease generalisable to those with Philadelphia positive disease?	Results from the ELIANA, ENSIGN and B2101J clinical trials do not report outcomes for Philadelphia chromosome-positive (*BCR-ABL1*) ALL patients specifically, as the number of patients with this specific disease type were so small (analyses were only to be performed if at least five patients were present in each subgroup). However, subgroup analyses were conducted for overall remission rate (ORR) in ELIANA and ENSIGN for patients with a range of genetic abnormalities, including those with Philadelphia chromosome-positive ALL, as well as those with *MLL* rearrangement, hypodiploidy, *BCR-ABL1*-like gene signatures and complex karyotypes (≥5 unrelated abnormalities). The results of these analyses were consistent with those of the full analysis set (FAS) in both ELIANA and ENSIGN, with high response rates (ORR was [redacted] in both trials for patients with genetic abnormalities), demonstrating that the efficacy associated with tisagenlecleucel is consistent irrespective of the presence of genetic abnormalities such as the Philadelphia chromosome; therefore, the results achieved in the tisagenlecleucel clinical trials overall can be considered generalisable to patients with Philadelphia chromosome-positive disease.
Question 2: What is the treatment pathway for people younger than 18 years of age with primary refractory B-cell ALL?	
Do people younger than 18 years of age with primary refractory B-cell ALL routinely receive treatment based on the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol?	No. Based on UK clinical expert feedback, patients under the age of 18 years with primary refractory B-cell ALL *do not* routinely receive treatment based on the NOPHO protocol. As there are so few patients with primary refractory ALL, and a lack of clinical guidelines in the UK for these patients specifically, choice of treatments vary between individual patients and treatment centres and there is not one universally-used protocol. The clinical experts consulted at the time of writing the company submission did not mention the NOPHO protocol for primary refractory patients. Their feedback was that FLA-IDA and blinatumomab are primarily used as potential treatment options for these patients in current clinical practice. Therefore, it is not the case that patients with primary refractory ALL routinely

	receive treatment based on the NOPHO protocol in England, and instead several treatment options may be tried in this setting.
Is the company's position of tisagenlecleucel-T in the treatment pathway for people younger than 18 years of age with primary refractory disease appropriate?	Primary refractory patients were eligible for inclusion within the ELIANA, ENSIGN and B2101J clinical trials if they had primary refractory ALL as defined by not achieving a complete remission (CR) after two cycles of a standard chemotherapy regimen. These patients are also included within the anticipated licence for tisagenlecleucel. Therefore, there is no reason to suggest that these patients would not be eligible for tisagenlecleucel in UK clinical practice at this point in the treatment pathway. In addition, the fact that there are existing, effective treatments for patients with primary refractory disease does not preclude the use of tisagenlecleucel in primary refractory patients, nor the ability for tisagenlecleucel, as a novel agent, to displace current practice.
Question 3: What is the current treatment pathway for people with B-cell ALL with 2 or more disease relapses?	
Where is blinatumomab used in the current treatment pathway for Philadelphia negative disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	**Patients <18 years:** feedback from UK clinical experts at the time of writing the company submission was that the vast majority of patients <18 years of age with B-cell ALL receive treatment according to the ALLR3 protocol following a first relapse, and blinatumomab is most commonly reserved for use following two or more relapses. In recent weeks however, paediatricians at Great Ormond Street Hospital have started to use blinatumomab as an option to treat high risk patients in first relapse (although it is our understanding that many other centres still treat according to the ALLR3 protocol). When used following a first relapse, the feedback from clinical experts at Great Ormond Street Hospital was that blinatumomab would typically be given for one cycle or occasionally two cycles (compared with the 5 of 6 cycles that would be required following 2 or more relapses). As only 1 or 2 cycles of blinatumomab would be given in this setting, the possibility of CD-19 escape is negligible and therefore the use of blinatumomab at this stage would not preclude the use of further blinatumomab or indeed the use of tisagenlecleucel following a second relapse. **Patients >18 years:** In some centres blinatumomab may be offered earlier on in the treatment pathway, following a first relapse. In other centres, patients are treated with blinatumomab following two or more disease relapses.

Is blinatumomab an appropriate comparator to tisagenlecleucel-T for relapsed disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	Blinatumomab is an appropriate comparator for patients both <18 years and >18 years as it is a treatment option offered to patients at an equivalent point in the treatment pathway to where tisagenlecleucel is anticipated to be placed. This is supported by feedback from UK clinical experts who confirmed that blinatumomab, along with salvage chemotherapy (FLA-IDA), were the current standards of care for paediatric and young adult patients with a second or later relapse of ALL in both age groups. Although blinatumomab may be offered to some patients following a first relapse, this does not preclude its use at a later treatment line. Therefore, blinatumomab remains a comparator to tisagenlecleucel at second or later relapse. Furthermore, feedback from UK clinical experts was that the use of one or two cycles of blinatumomab following a first relapse would be highly unlikely to result in a CD19-negative relapse, and therefore the use of blinatumomab at this stage would not preclude the use of tisagenlecleucel following a second relapse.
Question 4: Is it appropriate to use clofarabine as a proxy for the efficacy of FLA-IDA (that is salvage chemotherapy)?	
Is clofarabine used in clinical practice in the NHS in England?	Feedback from UK clinical experts is that clofarabine is used very rarely in UK clinical practice. Although it has been approved by the EMA for the treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response, the consensus from UK clinical experts was that the toxicity profile of clofarabine was inappropriate for use in the majority of patients. Therefore, clinicians choose to use FLA-IDA, which they consider to be as effective as clofarabine but associated with less toxicity.
Is there any evidence to support the equivalence of FLA-IDA and clofarabine?	In the absence of any relevant trials evaluating FLA-IDA, Novartis sought expert clinical feedback in order to produce a comparison versus salvage chemotherapy within the company submission. Four UK clinical experts were consulted as part of this appraisal and all four agreed that the efficacy of clofarabine monotherapy observed in the Jeha *et al.* (2006) trial were consistent with outcomes observed in clinical practice and could be considered reflective of FLA-IDA. In addition, Jeha *et al.* (2006) was selected as the efficacy source for standard of care chemotherapy in the mock appraisal of CAR-T therapies conducted by the University of York. Novartis fully acknowledge that the use of Jeha *et al.* (2006) as a proxy for the efficacy of FLA-IDA is associated with uncertainty and therefore conducted several scenario analyses evaluating different sources of data for the efficacy of FLA-IDA within the company submission, namely; von

	Stackelberg *et al.* 2011, Kantarjian *et al.* 2017 (both of which investigated a mixture of chemotherapy regimens) and Hijiya *et al.* 2011 (clofarabine, etoposide and cyclophosphamide). These scenarios were not associated with significant changes to the base case results of the economic model, with ICERs (with PAS) for tisagenlecleucel versus salvage chemotherapy of £20,890, £26,743 and £27,615, respectively, compared to the base case ICER of £25,404. Therefore, Novartis believe we have made every effort to produce as robust a comparison versus salvage chemotherapy as was possible, and have accompanied this with several scenarios to explore any potential uncertainty. Based on these results, the ICERs versus salvage chemotherapy when using the various sources of efficacy data consistently remained below a cost-effectiveness threshold of £30,000 per QALY gained. Finally, it is important to note that the ERG's preferred source of efficacy data for salvage chemotherapy (Kuhlen *et al.* 2017) is associated with several limitations: • The proportion of patients with a previous allo-SCT was 100% in Kuhlen versus 54.2% in the tisagenlecleucel trials, hence it has only been conducted in a subset of the population potentially eligible for tisagenlecleucel and the Jeha 2006 study is therefore more inclusive of the overall population. However, 26.3% of patients received a further subsequent SCT. Second SCTs are extremely rare in the UK in this patient population, which raises questions about the representativeness of this study to UK practice. The high rate of SCT is biasing results against tisagenlecleucel as SCT is a curative option and therefore OS in this study is a clear overestimate. • Patients with extramedullary relapse (which are shown to have statistically significantly better outcomes for both OS and EFS) were excluded from the tisagenlecleucel trials, but represent 19.7% of the patient population in the Kuhlen et al. paper. • Finally, the HR for OS and EFS for T-ALL versus B-ALL (Table II in the Kuhlen study) was also not statistically significant and therefore it is misleading to state that there is a difference in outcomes between these groups. It is important to acknowledge when differences are not significant as this prevents misinterpretations of data. Non-significant data may result from chance rather than an actual observed difference. Taken together, Novartis believe these limitations discredit the Kuhlen study from being a more appropriate source of efficacy data than the Jeha 2006 study used within the company submission.

Question 5: Long term usage and costs of IVIG treatment - real world experience	
Would people younger than 18 years of age require continued IVIG treatment and for how long?	Consensus from several UK clinical experts consulted in response to this question was that a lifetime duration of IVIG is clinically implausible and the duration of IVIG treatment in patients <18 years of age would be aligned with the duration of B-cell aplasia; the estimate of 11.4 months used in the base case of our submission (which was based on the time to B-cell recovery), was therefore validated by UK clinical experts and is considered appropriate. Clinical experts also stated that when paediatric patients transition to the adult population (i.e. >18 years of age), they would be treated according to the adult protocol (see below). This involves the receipt of IVIG only if a patient has B-cell aplasia alongside a severe infection or severe cytomegalovirus (CMV) reactivation. This only occurs in approximately 20% adult patients, and patients would be treated with IVIG for 6-12 months only.
Would people aged 18-25 years require continued IVIG treatment and for how long?	As highlighted above, patients with r/r B-cell ALL aged 18–25 would not receive continued IVIG treatment following infusion with tisagenlecleucel. Feedback from UK clinical experts sought in response to this question was that patients will only receive treatment with IVIG if they have B-cell aplasia alongside a severe infection or severe CMV reactivation. This only occurs in approximately 20% adult patients, and patients would be treated with IVIG for 6-12 months only. It should be noted that this feedback was received after the company submission to NICE, and therefore the assumptions made within the company base case with regards to the administration of IVIG were conservative.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed response form

Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK

Appendix

Re: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) in people aged up to 25 years [ID1167] – updated data cut-off from the ELIANA clinical trial

Latest data cut-off from the ELIANA clinical trial (13th Apr 2018)

The latest data cut-off from ELIANA (13th Apr 2018) is the second presented to the Committee, following the initial data cut-off (31st Dec 2017), which were presented in the initial company submission. A summary of the latest data cut-off (13th Apr 2018) compared to that presented in the company submission (31st Dec 2017) is presented below in Table 1. As is evident in Table 1, the results from the updated data cut-off (13th Apr 2018) are consistent with those from the data cut-off presented within the company submission (31st Dec 2017). These data highlight the robustness of the data presented initially, and continue to support the clinical benefits of tisagenlecleucel in paediatric and young adult patients with ALL and the assumptions upon which the economic analysis within the company submission were based.

All data from the 31st Dec 2017 and 13th Apr 2018 data cut-offs for the ELIANA clinical trial are academic in confidence and should remain confidential.

Table 1: Overview of clinical effectiveness results from the ELIANA clinical trial

n (%)	ELIANA 31st Dec 2017 (N=79) (N=77 for ORR and DoR)[a]	ELIANA 13th Apr 2018 (N=79)
Primary efficacy results		
BOR[b]		
ORR (CR+CRi) (95% CI; p value)	[redacted]	[redacted]
CR	[redacted]	[redacted]
CRi	[redacted]	[redacted]
NR/Unknown[d]	[redacted]	[redacted]
ORR with bone marrow MRD negative (i.e. MRD <0.01%) (95% CI; p value)	[redacted]	[redacted]
Secondary efficacy results		
DoR (/RFS)		
% event free at 6 months (95% CI)	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]
EFS		

% event free at 6 months (95% CI)	[redacted]	[redacted]
% event free at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]
OS		
% at 6 months (95% CI)	[redacted]	[redacted]
% at 12 months (95% CI)	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]

[a]ORR and DoR from the 31st Dec 2017 data cut-off for the ELIANA clinical trial were assessed in patients at least 3 months post-tisagenlecleucel infusion only (efficacy analysis set). [b]BOR is reported within 3 months for the ELIANA clinical trial. [c]No formal significance testing was conducted as the endpoint was met at the interim analysis. Nominal p-value is presented. [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.

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete remission; CRi: CR with incomplete blood count recovery; DoR: duration of remission; MRD: minimum residual disease; NE: not estimable; NR: non-responder/no remission; ORR: overall remission rate

Source: ELIANA CSR (31st Dec 2017);[1] ELIANA CSR (13th Apr 2018).[2]

Event-free survival

At the latest data cut-off (13th Apr 2018), in the full analysis set (FAS), [redacted] of the [redacted] patients (39.2%) per IRC review reported treatment failure, relapse or death due to any cause after remission prior to the data cut-off. The median EFS was [redacted]. The estimated event-free probability was [redacted] (95% CI: [redacted]) at Month 6 and [redacted] (95% CI: [redacted]) at Month 12 and Month 18. The Kaplan-Meier plot for EFS per IRC assessment is presented in Figure 1.

Figure 1. Kaplan-Meier Plot for EFS censoring allo-SCT by IRC assessment in the ELIANA clinical trial (13th Apr 2018; FAS)

[redacted]

Abbreviations: allo-SCT: allogeneic stem cell transplantation; CI: confidence interval; EFS: event-free survival; FAS: full analysis set; IRC: Independent Review Committee; NE: not estimable.

Source: ELIANA CSR (13th Apr 2018).[2]

Overall survival

At the latest data cut-off (13th Apr 2018), in the FAS, [redacted] patients ([redacted]) died after tisagenlecleucel infusion and the estimated probability of survival was [redacted] (95% CI: [redacted]) at Month 6, [redacted] (95% CI: [redacted]) at Month 12 and [redacted] (95% CI: [redacted]) at Month 18. Median OS was [redacted]. The Kaplan-Meier plot for OS is presented in Figure 2.

Figure 2: Kaplan-Meier plot for OS in the ELIANA clinical trial (13th Apr 2018; FAS)

Abbreviations: CI: confidence interval; FAS: full analysis set; NE: not estimable; OS: overall survival.
Source: ELIANA CSR (13th Apr 2018).[2]

References

1. 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.
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 (13th April 2018 data cut-off). Data on File. 2018.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 3 to 25 years [ID1167]

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Deadline for comments **12pm Monday 13 August 2018** email: **tacommc@nice.org.uk /NICE DOCS**

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About you

Your name	**Prof Peter Clark**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England**
Are you (please tick all that apply)	☐ a representative from the company (Novartis)? ☐ a clinical expert? **x** a commissioning expert? ☐ a patient expert or organisation? **x** an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Questions for engagement

Question 1: What population are likely to receive tisagenlecleucel-T for relapsed or refractory B-cell ALL in clinical practice?	
Is tisagenlecleucel likely to be used for people with Philadelphia positive disease?	Yes. The Ph pos ALL population is very small in young patients with ALL and there is no biologically plausible reason as to why such patients would not be treated with T-L CAR T cell therapy. NHS England notes that such patients were included in the T-L trials.
Are the results for Philadelphia negative disease generalisable to those with Philadelphia positive disease?	See above

Question 2: What is the treatment pathway for people younger than 18 years of age with primary refractory B-cell ALL?	
Do people younger than 18 years of age with primary refractory B-cell ALL routinely receive treatment based on the Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocol?	Yes. The numbers of patients with disease refractory to 1st line therapy are small and were also small in the T-L trials. NHS England observes that the current standard treatment for disease refractory to 1st line induction in those aged 18 years or less is mainly using the NOPHO protocol. This was not recognised in the company's submission. For those aged over 18 years (a much smaller group), the current treatment is blinatumomab or combination chemotherapy and more likely to be blinatumomab. Thus there is some current blinatumomab use in this population although this will soon be displaced by inotuzumab.
Is the company's position of tisagenlecleucel-T in the treatment pathway for people younger than 18 years of age with primary refractory disease appropriate?	NHS England concludes that the comparator for 1st line refractory patients aged 18 yeasr or less should be mainly the NOPHO protocol as this is used in children and teenagers. Currently, there is also some blinatumomab use in young adults but such use of blinatumomab is likely to diminish in favour of inotuzumab.
Question 3: **What is the current treatment pathway for people with B-cell ALL with 2 or more disease relapses?**	
Where is blinatumomab used in the current treatment pathway for Philadelphia negative disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	For patients who respond to 1st line induction and then relapse, the aim of treatment is attain a second remission and then consolidate this with an allogeneic SCT. For patients who relapse post-SCT, the company has stated that the standard comparators are either combination cytotoxic chemotherapy FLA(G)-IDA or the CD19-targeted monoclonal antibody blinatumomab. The company states that FLA(G)-IDA and blinatumomab are also the comparators for patients in 2nd or further relapse. Blinatumomab is a specific T-cell engager antibody which binds specifically to CD19 expressed on the surface of cells of B-lineage and also to CD3 expressed on the surface of T cells. It thus activates T cells by connecting the CD3 on the T cell with CD19 on benign and malignant B cells. Blinatumomab is recommended by NICE as a treatment

	option in adults with relapsed/refractory Philadelphia chromosome negative ALL. Blinatumomab access has been extended to the non-adult ALL population by NHS England. The administration of blinatumomab is inconvenient and demanding for patients and clinical staff. Of note too is that approximately 22% of patients who relapse post blinatumomab do so with ALL which no longer expresses CD19. T-L CAR T cell therapy also targets CD19 and as a consequence there is therefore a concern that patients previously treated with blinatumomab and who then relapse may have clones of B cells which do not express CD19. In such circumstances, treatment with T-L would therefore not be expected to have any significant chance of curing the patient. The 3 T-L trials excluded patients previously treated with blinatumomab and thus there is no evidence of the efficacy of T-L in patients previously treated with blinatumomab. As a consequence of the biological plausibility of prior blinatumomab reducing the benefits of CAR T cell treatment directed at CD19 plus the exclusion of patients with prior blinatumomab exposure in the T-L trials, there will be wariness by haematologists in the use of blinatumomab if CAR T cell therapy with T-L is a potential salvage therapy later in the treatment pathway. Although combination chemotherapy and blinatumomab were commissioned options for relapsed/refractory ALL at the times of the NICE scope and the Novartis and ERG submissions, inotuzumab ozogamicin is now NICE-recommended in adults with relapsed/refractory ALL and funding has been extended to children by NHS England. Inotuzumab is directed against CD22 and thus does not carry any biological plausibility in potentially reducing the benefits of subsequent T-L therapy. In addition, it is a much more convenient drug to receive and deliver than blinatumomab. Hence it is likely to rapidly displace much use of blinatumomab and especially so in the relapsed/refractory ALL population in which CAR T cell therapy with T-L could be an option later in the treatment pathway. The administration costs of inotuzumab are much less than for blinatumomab and it is likely that drug procurement costs (based on the list prices of the two drugs) will also result in inotuzumab costing less than blinatumomab. As inotuzumab results in

	higher rates of CR and SCT than combination chemotherapy at 1st relapse, it is likely to become the treatment of choice at this place in the treatment pathway. NHS England notes that that at the time of the NICE scope, NICE stated that the comparators for T-L should be 'established clinical management without T-L'. NICE did list the inotuzumab appraisal in the March 2018 scope as an appraisal in development. Although NHS England recognises that inotuzumab is not yet in August 2018 a part of 'established clinical management', it will become so in the very near future given its obvious practical advantages. For the much larger T-L eligible populations of relapsed post-SCT and in 2nd or further relapse that have not had SCT, the comparator options are currently the same treatments in these 2 places in the treatment pathway and depend on what has been used previously – if chemotherapy is used at 1st relapse, then the comparator at 2nd relapse would be blinatumomab (though shortly to be inotuzumab); if blinatumomab is used at 1st relapse (and shortly to be replaced by inotuzumab), then the comparator for 2nd relapse would be chemotherapy, the most commonly used regimen being FLA(G)-IDA or the ALLR3 protocol (which is similar to FLA-IDA although given for longer) or the combination of clofarabine, cyclophosphamide and etoposide. As has been stated above, treatment for 1st line relapse is likely to become inotuzumab in the near future and hence these same 2 options of blinatumomab and FLA(G)-IDA apply as comparators for T-L. There is little data on the use of blinatumomab after previous inotuzumab although there is no biologically plausible reason as to why blinatumomab should not be active. However this lack of evidence may affect the choice of treatment.
Is blinatumomab an appropriate comparator to tisagenlecleucel-T for relapsed disease: • *for people younger than 18 years of age?* • *for people aged 18-25 years?*	See above

Question 4: Is it appropriate to use clofarabine as a proxy for the efficacy of FLA-IDA (that is salvage chemotherapy)?	
Is clofarabine used in clinical practice in the NHS in England?	Clofarabine is used but in combination chemotherapy ie not as monotherapy.
Is there any evidence to support the equivalence of FLA-IDA and clofarabine?	NHS England notes that Novartis used clofarabine monotherapy data as the proxy for combination chemotherapy with FLA-IDA. The clofarabine data was use of clofarabine monotherapy, not combination treatment (single-agent cytotoxic chemotherapy is very rarely used in acute leukaemia). The clofarabine monotherapy data was old, the first patient being treated in 2002 and the data cut off was in September 2004. Supportive care has changed much since 2002-2004 with significantly improved outcomes, including in the access to and the speed of access to SCT donors. This therefore means that the outcomes in the clofarabine monotherapy dataset are likely to be inferior to those of the combination FLA-IDA given in in a more contemporaneous time. The indirect comparison of the pooled T-L studies with old clofarabine monotherapy data used as a proxy for FLA-IDA is inappropriate as there is more contemporaneous data for FLA-IDA (according to the ERG) with greater numbers of patients and longer median duration of follow-up. The heterogeneity of the data in any indirect comparisons of T-L with chemotherapy and also with blinatumomab is noteworthy.
Question 5: Long term usage and costs of IVIG treatment - real world experience	
Would people younger than 18 years of age require continued IVIG treatment and for how long?	A significant side-effect is hypogammaglobulinaemia. B-cell ablation is a pharmacodynamic measure of successful treatment with CAR-T cell products directed against leukaemia of B-cell origin. Loss of circulating B-cells and consequent drastic falls in serum immunoglobulin (Ig) levels, also known as agammaglobulinaemia, is a predictable on-target off-tumour effect of T-L. The pivotal study on T-L in children and young adults with refractory acute lymphoblastic leukaemia (Maude et al. New Eng J Med 2018;378:439-48) showed that all patients

	responding to CAR-T cells developed B-cell aplasia and *most* of these 75 patients (exact number not specified) received IVIg. The probability of B cell recovery was [redacted] at 12 months but NHS England notes that this figure did not change at [redacted] months (albeit based on small numbers). From the point of view of a clinician looking after these highly immunosuppressed patients who all undergo conditioning chemotherapy prior to CAR-T cell treatment, there is bound to be considerable anxiety associated with merely observing a patient with no circulating B cells and Ig, as opposed to intervening with prophylactic Ig. Until there is solid longitudinal data on the infection risks associated with CAR-T cell associated agammaglobulinaemia, there is bound to be great and clinically justifiable pressure to use prophylactic Ig. Whilst it is not expected that every patient who receives a B-cell directed CAR-T cell treatment will require IVIg, it is predicted that the majority of responders to CAR-T cells will do so. For the purposes of costing IVIg requirements, long term follow up data on the proportion of patients who developed B-cell aplasia and low Igs as a consequence of CAR-T cell therapy is required. Until that is known, a pragmatic estimate of that up to 50% of responders will require IVIg (until B cell aplasia recovers) for a period of 12-24 months would not be unreasonable. As regards route of delivery, both intravenous Ig (IVIg) and subcutaneous Ig (SCIg) would be equally efficacious. Given that CAR-T cell therapy will be limited to major haematology centres, it is expected that the majority of those patients requiring Ig will be able to undergo training for home administration of SCIg. IVIg and SCIg are costly interventions and thus could have a significant impact on the mean cost of the supportive care that has to be wrapped around each patient who responds to T-L.

Would people aged 18-25 years require continued IVIG treatment and for how long?	

Thank you for your time.

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