Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]

Contents:

The following documents are made available to stakeholders:

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

1. **Company full submission** from Bristol-Myers Squibb

2. **Company summary of information for patients (SIP)** from Bristol-Myers Squibb

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Blood Cancer UK
   b. Lymphoma Action

5. **Expert personal perspectives** from:
   a. Dr Wendy Osborne – clinical expert, nominated by Bristol-Myers Squibb
   b. Professor Christopher Fox - clinical expert, nominated by the Association of Cancer Physicians
   c. Christopher Strange – patient expert, nominated by Blood Cancer UK

6. **External Assessment Report** prepared by Warwick Evidence

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Document B

Company evidence submission

12th August 2024

File name	Version	Contains confidential information	Date
ID3887_Liso-cel in LBCL_Document B_FINAL_12Aug24_CON	**FINAL**	Yes	12th August 2024

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Abbreviations

Abbreviations	Definition
1L	First-line
2L	Second-line
3L(+)	Third-line (plus)
ABC	Activated B-cell like
ACM	Appraisal committee meeting
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogenic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
Axi-cel	Axicabtagene ciloleucel
BCMA	B-cell maturation antigen
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criterion
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medical Products for Human Use

Abbreviations	Definition
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	Cyclophosphamide, doxorubicin and prednisone
CI	Confidence interval
CII	Cost Inflation Index
CNS	Central Nervous System
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CUA	Cost utility analysis
DCO	Data cut off
DHAP	Dexamethasone, cytarabine, cisplatin
DHAX	Dexamethasone, cytarabine and oxaliplatin
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EBV	Ebstein-Barr Virus
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Event-free
EFS	Event-free survival
EMA	European Medicines Agency
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study
ESHAP	Etoposide, methylprednisolone, high dose cytarabine and cisplatin
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FISH	Fluorescence in situ hybridisation
FLBCL	Follicular large B-cell lymphoma
GCB	Germinal centre B-cell
GDP	Gemcitabine, dexamethasone and cisplatin
GEMOX	Gemcitabine and oxaliplatin
GP	General practitioner
HCRU	Healthcare resource use
HDCT	High dose chemotherapy
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HMRN	Haematology Malignancy Research Network
HR	Hazard ratio
HRQOL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
HTA	Health Technology Assessment
ICE	Ifosfamide, carboplatin and etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IHC	Immunohistochemistry
INHB	Incremental net health benefit
IPD	Individual patient data
IPI	International Prognostic Index
IQR	Interquartile range

Abbreviations	Definition
IRC	Independent review committee
IRR	Infusion Related Reaction
IRT	Interactive Response Technology
ITT	Intention to treat
IVE	Ifosfamide, etoposide and epirubicin
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
LFT	Liver function test
Liso-Cel	Lisocabtagene maraleucel
LVEF	Left ventricular ejection fraction
LYG	Life years gained
LYM	Lymphoma
MAIC	Matching adjusted indirect comparison
MAS	Macrophage activation syndrome
MCM	Mixture cure model
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimal Important Difference
MUGA	Multi-gated acquisition scan
MYC	Myelocytomatosis oncogene
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NEC	Not elsewhere classified
NHB	Net health benefit
NHL	Non Hodgkin's lymphoma
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NR	Not reported
ONS	Office for National Statistics
ORR	Overall Response Rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PICO	Population, Intervention, Comparators, Outcomes
PMBCL	Primary Mediastinal B-cell lymphoma
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QOL	Quality of life
R-	Rituximab
RCT	Randomised controlled trial
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event

Abbreviations	Definition
SAS	Safety analysis set
SCT	Stem cell transplantation
SD	Stable disease / standard deviation
SE	Standard error
SLE	Systemic lupus erythematous
SLR	Systemic literature review
SMR	Standardised mortality ratio
SOC	Standard of care
SPD	Sum of products of diameters
STM	State transition model
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
tFL	Transformed follicular lymphoma
THRBCL	T-cell histiocyte rich large B-cell lymphoma
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor
TSD	Technical Support Document
TTNT	Time to next treatment
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

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

B.1.1 *Decision problem*

[redacted]

Liso-cel is licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of adult patients with relapsed or refractory (R/R) DLBCL, PMBCL and FL3B after two or more lines of systemic therapy.[1] The treatment of liso-cel in this indication (ID1444) was previously evaluated by the National Institute for Health and Care Excellence (NICE), but the appraisal was suspended following the first appraisal committee meeting (ACM).[2]

The population considered in this submission is adult patients with DLBCL, HGBCL, PMBCL or FL3B who are eligible for stem cell transplantation (SCT) and who relapsed within 12 months from completion of, or are refractory to, first-line immunochemotherapy (referred to as early relapsed/primary refractory hereafter). This represents a subpopulation of the anticipated licensed indication to align with the population eligible for SCT included in the TRANSFORM Phase III randomised controlled trial (RCT), which provides the pivotal evidence base for this submission. For simplicity and brevity, DLBCL, HGBCL, PMBCL and FL3B will be referred to as large B-cell lymphoma (LBCL) hereafter; while other LBCL types do exist, these additional types are not included in the licence for liso-cel and are therefore not considered in this submission.

Data on LBCL, including the rarer subtypes of PMBCL, HGBCL and FL3B are limited. Given that the disease characteristics and treatment pathways of these rarer subtypes of lymphoma are similar to DLBCL in the second-line setting and that data in these subtypes are limited, the following sections primarily focus on data for DLBCL.

In this population, liso-cel would displace current second-line standard of care (SOC) of re-induction immunochemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) in responding patients. In this submission, the term ‘SCT’ will be used when describing the eligibility of patients and ‘ASCT’ will be used when referring to the intervention. The decision problem addressed within this submission is 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 with relapsed or refractory aggressive B-refractory DLBCL, HGBCL, PMBCL or FL3B after 1 prior therapy	Adults with early (≤ 12 months) relapsed/primary refractory DLBCL, PMBCL, HGBCL or FL3B who are eligible for SCT	The population included in the final scope is broader than the TRANSFORM trial in the following two aspects: • Only patients with early relapsed (within 12 months)/primary refractory disease are included in TRANSFORM, in line with license for liso-cel • Only patients eligible for SCT enrolled in the TRANSFORM trial The population considered for this submission is therefore narrower than the NICE final scope. This represents a subpopulation of the anticipated licensed indication in order to align with the population included in the pivotal TRANSFORM trial, which enrolled only patients who were eligible for SCT and had early relapsed/primary refractory disease. Liso-cel is also being evaluated for the treatment of relapsed or refractory (R/R) LBCL patients who are ineligible for HDCT and ASCT (SCT-ineligible) in the Phase II trial TRANSCEND-PILOT (NCT03483103).[3] This population is not included in this submission and will be appraised separately, in order to align this submission with the population included in the TRANSFORM trial and licence for liso-cel in this indication.

Intervention	Lisocabtagene maraleucel	Lisocabtagene maraleucel	In line with the NICE final scope.
Comparator(s)	Established clinical management without lisocabtagene maraleucel, including but not limited to: • Immunotherapy with HDCT with or without ASCT • Polatuzumab vedotin with rituximab and bendamustine (Pola+BR; if haematopoietic stem cell transplant is not suitable)	SOC re-induction therapy (R-DHAP [rituximab, dexamethasone, cytarabine, cisplatin], R-ICE [rituximab, ifosfamide, carboplatin, etoposide], R-GDP [rituximab, gemcitabine, dexamethasone, cisplatin]) followed by HDCT and ASCT in responders	There are several re-induction therapies available in the UK. In this appraisal, only R-DHAP, R-ICE and R-GDP are considered as relevant comparators, as these regimens are deemed the most routinely or commonly used in UK clinical practice, according to feedback received from UK clinical experts. Additionally, as the population for this submission is patients who are eligible for SCT, Pola+BR is not considered a relevant comparator as it is licensed for those who are not suitable for ASCT (TA649).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • event-free survival • response rates • adverse effects of treatment • health-related quality of life	All outcomes specified in the NICE final scope are included in the submission as follows: • event-free survival (time from randomisation to death from any cause, progression, failure to achieve complete response or partial response by 9 weeks post-randomisation or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first) • overall survival (time from randomisation to time of death due to any cause) • progression-free survival (time from randomisation to progression, or death from any cause, whichever occurs first)	Event-free survival (EFS) is the primary endpoint from the TRANSFORM trial.[4] For early relapsed/primary refractory LBCL, this endpoint is more clinically relevant than progression-free survival (PFS) given the curative intent of treatment. In this indication, 'stable disease' is not considered a successful treatment outcome and, therefore, patients who remain progression-free but with stable disease are moved on to receive a subsequent treatment line. In TRANSFORM, these patients could crossover into the liso-cel arm and, as a result, any comparison of progression-free survival between liso-cel and standard of care is likely to be biased. In line with the approach taken in TA895, EFS will therefore be used alongside

		• progression-free survival on next line of therapy (time between randomisation to progressive disease on the next line of subsequent treatment or death from any cause)
		• response to treatment, including:
		  ○ complete response rate (percentage of patients achieving a complete response)
		  ○ duration of response (time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause)
		  ○ overall response rate (percentage of patients achieving an objective response of partial response or better)
		• adverse effects of treatment
		• health-related quality of life using the global health/quality of life, fatigue, physical and cognitive functioning subscales of the EORTC QLQ-C30, the FACT-LymS and EQ-5D
			overall survival (OS) and health-related quality of life (HRQoL) data to capture the most important health related benefits of liso-cel in the cost-effectiveness modelling.[5]

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should	• The cost-effectiveness of liso-cel versus SOC has been evaluated, in line with the NICE	In line with the NICE final scope

	be expressed in terms of incremental cost per quality-adjusted life year. 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	reference case • A lifetime horizon has been adopted within the analysis to sufficiently reflect any differences in costs between the technologies being compared • Costs were considered from an NHS and Personal and Social Services perspective (PSS) • A patient access scheme (PAS) for liso-cel was included in the analysis	

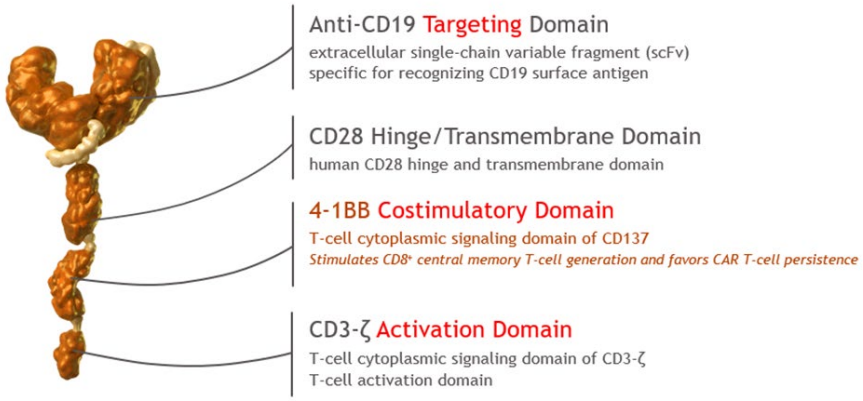
Abbreviations: ASCT: autologous stem cell transplant; HDCT: high-dose chemotherapy; LBCL: large B-cell lymphoma; NHS: National Health Service; R-DHAP: rituximab-dexamethasone, cytarabine, cisplatin; R-GDP: rituximab- gemcitabine, dexamethasone, cisplatin; R-ICE: rituximab-ifosfamide, carboplatin, etoposide; SOC: standard of care.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with liso-cel for the treatment of patients with early relapsed/primary refractory LBCL who are eligible for SCT is presented in Table 2.

Links to the MHRA and EU Summary of Product Characteristics (SmPC) for liso-cel are provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Lisocabtagene maraleucel (liso-cel; Breyanzi®)
Mechanism of action	Liso-cel is a CD19 directed genetically modified autologous cellular immunotherapy which targets CD19-expressing cells, including B-cell malignancies, using similar mechanisms to that of cytotoxic T-cells. **Structure** As part of the liso-cel manufacturing process, the patient's T-cells are harvested by leukapheresis, where peripheral blood monocyte cells are separated from the patient's blood via an apheresis machine. The patient's T-cells are then genetically modified using a replication incompetent lentiviral vector, to express a chimeric antigen receptor (CAR) construct. Liso-cel contains an external target-binding anti-CD19 domain responsible for recognising the lymphoma cells, a CD28 transmembrane domain, an internal CD3 zeta signalling domain and 4-1BB co-stimulatory domain. The activation domain initiates T-cell activation (Figure 1), enabling the induction of malignant cell death and the co-stimulatory domain allows more potent signalling which improves T-cell activation, anti-cancer activity and CAR-T cell persistence.[7,6] **Figure 1: Structure of liso-cel**  **Abbreviations:** CAR: chimeric antigen receptor; scFv : single chain variable fragment. **Sources:** Makita et al. (2019)[7]; Teoh et al. (2019)[8]; Jayaraman et al. (2020)[9]; Weinkove et al. (2019)[10]. **Manufacturing** Liso-cel has a highly controlled manufacturing process that, unlike other CAR T-cell therapies, enables administration of a defined composition with a precise dose of CD8+ and CD4+ CAR T-cells. Each T-cell population (CD4+

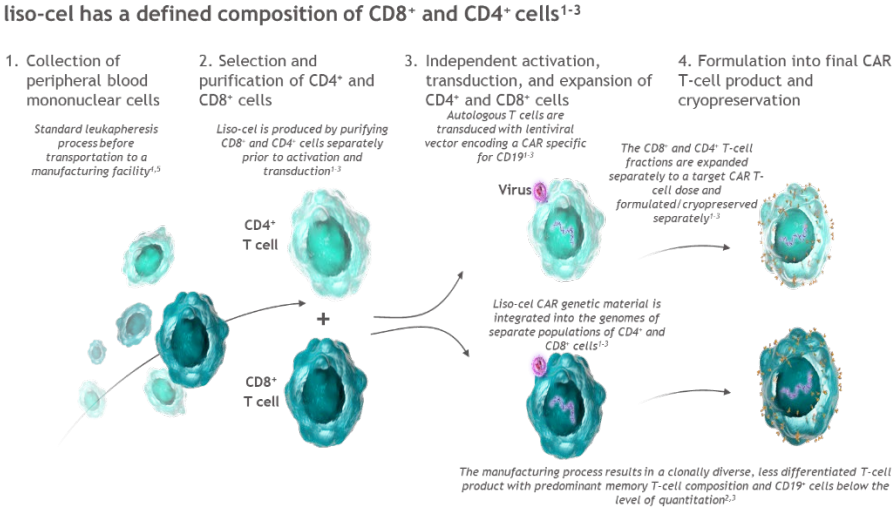
and CD8+) is transduced and expanded separately under conditions optimised for each cell type, in contrast to other CAR T-cell therapies where an uncontrolled mixture of CD4+ and CD8+ CAR T-cells are transduced and expanded. Once expanded, each population is purified to ensure a fixed number of CAR+ T-cells. Liso-cel is then administered as two separate infusions of CD8+ and CD4+ CAR T-cells at a fixed 1:1 ratio (Figure 2).[7, 11]

The presence of CD4+ T-cells is known to promote CD8+ effector T-cell expansion, memory formation, and trafficking to antigen-rich tissues to mediate antitumour effector function. Furthermore, CD4+ T-cells aid in the survival of activated CD8+ T-cells and are required for establishing CD8+ T-cell memory.[12, 13] In preclinical models, CD19-directed CAR T-cells manufactured from purified CD8+ or CD4+ subsets resulted in superior antitumour reactivity in vivo compared with unselected T-cells.[14]

The manufacturing process and defined composition of liso-cel:[11, 15]

- Results in a consistently administered CD8+/CD4+ ratio minimising product variability and reducing the risk of complete manufacturing failure
- Prevents the transduction of other cell types
- May contribute to an improved safety and efficacy profile

Figure 2: Liso-cel manufacturing process



Sources: Ramsborg et al. (2017)[11];Teoh et al. (2019)[8]; Abramson et al. (2020)[16]; Hucks et al. (2019)[17] and Levine et al. (2016)[18]

Mechanism of action

The underlying mechanism of action of liso-cel involves preferentially targeting the CD19 antigen, a glycoprotein with near-universal expression on B-cell precursors and B-cells.[19, 20] Expression of CD19 is largely restricted to B lineage cells and is expressed in the majority of B-cell malignancies, including B-cell lymphomas.[21] Liso-cel is therefore able to target malignant cells whilst sparing non-cancerous cells from cytotoxicity, consequently limiting systemic effects.[22]

Once liso-cel binds to CD19-positive malignant B-cells, the CAR-T cell becomes activated and the cytotoxic potential of these cells is realised.[6] Death of malignant B-cells is primarily induced through CAR-mediated cytolysis (where target cells are killed due to destruction of the cell

	membrane), and the release of cytokines from the CAR-T cell.[23] Ligation of the CAR-T receptor also leads to CAR-T cell proliferation.[23]
Marketing authorisation/CE mark status	In March 2023, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of marketing authorisation for liso-cel for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line immunochemotherapy.[24] This marketing authorisation extension was accepted by the EMA on 28th April 2023. A marketing authorisation type II Variation extension application to the MHRA for a license in Great Britain was made in December 2023 via the EU Reliance Route for the treatment of [redacted]
Indications and any restriction(s) as described in the SmPC	Liso-cel is anticipated to be indicated for the treatment of: • [redacted] • adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy Contradictions to liso-cel include hypersensitivity to any of the excipients listed in section 6.1 of the SmPC. Contraindications of the lymphodepleting chemotherapy must also be considered.[1]
Method of administration and dosage	Liso-cel must be administered in a qualified treatment centre and treatment should be initiated under the direction of, and supervised by, a healthcare professional experienced in the treatment of haematological malignancies and trained on administration and management of patients treated with liso-cel. Tocilizumab and emergency equipment must be available prior to infusion of liso-cel and during the recovery period. Full details on the method of administration are provided in the SmPC (provided in Appendix C). **Method of administration and dosage** Liso-cel is intended for autologous use only and consists of a single dose IV infusion at the following target dosage: 100 x 10^6 CAR+ viable T cells within a range of 44–122 x 10^6 CAR+ viable T cells. As highlighted above, due to the highly controlled manufacturing process, a liso-cel dose consists of a 1:1 ratio of CD4+ and CD8+ cell components. The consistent CD8+/CD4+ ratio minimises product variability, reduces the risk of complete manufacturing failure and may contribute to an improved safety and efficacy profile compared to other CAR-T therapies. **Pre-treatment before liso-cel** Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day, should be administered intravenously for three days as a pre-treatment before liso-cel. Liso-cel is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy. It is also recommended that premedication with paracetamol and diphenhydramine (25-50 mg, intravenously or orally) or another H1-antihistamine, be administered 30 to 60 minutes before the infusion of liso-cel to reduce the possibility of an infusion reaction.

	The availability of liso-cel must be confirmed before starting the lymphodepleting chemotherapy regimen and patients should be clinically re-assessed prior to administration of both lymphodepleting chemotherapy and liso-cel.
Additional tests or investigations	As noted above, liso-cel must be administered in a qualified treatment centre.[1] All healthcare professionals who are expected to prescribe, dispense and administer liso-cel shall be provided with a healthcare professional guide, which will contain information about the identification and management of cytokine release syndrome (CRS) and serious neurological adverse reactions, among others.[1] **Monitoring and management after infusion** Patients should be monitored for the first 10 days following infusion at the qualified treatment centre for signs and symptoms of CRS, neurologic events and other toxicities. After the first 10 days following infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion.[1] CRS should be identified based on clinical presentation. Patients should be evaluated for, and treated, for other causes of fever, hypoxia, and hypotension. At least one dose of tocilizumab must be available per patient on site prior to infusion of liso-cel. The treatment centre should have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the MHRA Central Alerting System, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion. Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.[1] Patients should be counselled to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time, and these should be treated promptly. Intensive care supportive therapy should be provided for severe or life-threatening neurologic toxicities.[1] To aid with this, all patients who receive liso-cel are provided with a patient card, which contains information regarding the key adverse events (AEs) associated with liso-cel, relevant contact details and emphasises the need to report symptoms immediately.
List price and average cost of a course of treatment	The list price of one dose of liso-cel is £297,000.00. As liso-cel is administered as a one-time infusion, this is a one-time cost.
Patient access scheme (if applicable)	A confidential Patient Access Scheme (PAS) discount of [redacted]% to the liso-cel list price is available in UK practice, yielding to a net price for a single infusion of liso-cel of £[redacted]. Results within this submission are presented at PAS price.

Abbreviations: CAR: chimeric antigen receptor; CHMP: Committee for Medicinal Products for Human Use; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; EGFRt: truncated epidermal growth factor receptor; EMA: European Medicines Agency; FL3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; liso-cel: lisocabtagene maraleucel; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: patient access scheme; PMBCL: primary mediastinal large B-cell lymphoma; SmPC: summary of

product characteristics

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

Summary of the health condition

- Large B-cell lymphoma (LBCL) is a type of aggressive non-Hodgkin lymphoma (NHL) characterised by rapidly growing, abnormal B lymphocytes.[25, 26] Around 5,440 patients are newly diagnosed with LBCLs each year in the UK, corresponding to an annual incidence of 8.3 cases per 100,000 people (based on diagnoses between 2010 and 2019)[27, 28]
- Numerous subtypes of LBCL exist.[29] Diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B (FL3B) are the subtypes considered within this submission
- DLBCL is the most common type of NHL, accounting for around 40% of NHL cases.[30] PMBCL, FL3B and HGBCL are much less common than DLBCL, accounting for around 2–3%, 1%, and 1–2% of global NHL cases, respectively.[31, 32] Although the incidence of PMBCL, FL3B and HGBCL are low relative to DLBCL, they collectively represent a sizable proportion of patients
- Data on LBCL as a whole and the rarer types of LBCL, including PMBCL, HGBCL and FL3B are limited. Due to limited data across the rarer subtypes of LBCL, the following sections primarily focus on data for DLBCL, which is considered generalisable to all four types of LBCL in this submission, given that the disease characteristics and treatment pathways of each of these LBCL subtypes are similar at second-line (2L). For simplicity and brevity, DLBCL, PMBCL, HGBCL and FL3B will be referred to as LBCL hereafter[33]

Clinical outcomes

- LBCL is a curable disease, and approximately 60–70% of patients will be cured after receiving first-line (1L) therapy.[34, 35] However, a substantial proportion of patients will not be cured, because their disease does not respond to treatment (primary refractory LBCL), or because they experience disease relapse following completion of 1L treatment[35]
- Current standard of care (SOC) for 2L treatment of patients with early relapsed/primary refractory LBCL who are eligible for stem cell transplant (SCT) is platinum-based re-induction immunochemotherapy and subsequent high-dose chemotherapy (HDCT), followed by autologous SCT (ASCT) in responding patients to consolidate their response. Unfortunately, only approximately 50% of patients with early relapsed/primary refractory LBCL are eligible for SCT, and of these only around 50% actually go on to receive ASCT.[35-37] Furthermore, half of all patients treated with ASCT will experience further relapse and there is no guarantee of a cure.[35-37]
- Out of every 100 patients with early relapsed/primary refractory LBCL, it is estimated that only 50 will be eligible for SCT and only 10 patients will eventually be cured with current 2L SOC[38]
- Clinical outcomes are particularly poor among early relapsed/primary refractory LBCL patients, the focus of this submission. These patients experience a lower overall response rate (ORR) to re-induction therapy, are less likely to ever receive ASCT and experience reduced progression-free survival (PFS), event-free survival (EFS) and overall survival (OS) compared with patients who relapse >12 months after 1L therapy.[39, 40] The median EFS in the TRANSFORM and ZUMA-7 trials, including adult patients with early relapsed/primary refractory LBCL eligible for SCT, was just 2.4 months and 2.0 months in the SOC arms, respectively[5, 41]

Burden of disease

- Compared to the general population, the health-related quality of life (HRQoL) of patients with LBCL is considerably impaired by the symptoms of the disease, the psychological burden of receiving a cancer diagnosis and the side effects of the available treatments[42, 43]
- The current 2L SOC of re-induction therapy followed by HDCT and ASCT is also associated with considerable impact on HRQoL, and patients are at risk of several short- and long-term side effects, including infection, cardiac or pulmonary toxicity, anaemia and subsequent tumours[44]

UK treatment pathway for LBCL

- 1L treatment for LBCL generally involves rituximab-containing immunochemotherapy regimens with curative intent. According to UK clinical experts, most patients receive Pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisolone) in this setting[45]
- Current SOC for 2L treatment of patients eligible for SCT with early relapsed/primary refractory LBCL is platinum-based re-induction immunochemotherapy and subsequent HDCT and ASCT in responding patients to consolidate their response. Preferred re-induction regimens prior to HDCT and ASCT according to UK clinical experts include R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide)[45]
- At third-line and beyond (3L+), treatments for patients who relapse after ASCT or who are R/R to re-induction immunochemotherapy may include CAR T-cell therapy if eligible, or glofitamab, loncastuximab tesirine, epcoritamab or chemotherapy[45, 46]

Liso-cel

- Liso-cel is a CAR-T therapy anticipated to be licensed for use in [redacted]
- The TRANSFORM trial (the pivotal trial for liso-cel in this population, detailed in Section B.2) demonstrated that treatment with liso-cel would represent a step change in the treatment paradigm for patients with early relapsed/primary refractory LBCL versus SOC. Liso-cel resulted in statistically significant and clinically meaningful improvements in EFS, complete response rate (CRR) and PFS compared to SOC[41]
- In comparison to axicabtagene ciloleucel (axi-cel), a CAR-T therapy currently available via the Cancer Drugs Fund (CDF) for 2L early relapsed/primary refractory DLBCL patients, liso-cel is shown to be associated with a favourable safety profile. The results of a matching-adjusted indirect comparison (MAIC) found that liso-cel was associated with significantly lower odds of all-grade and Grade ≥ 3 cytokine release syndrome (CRS) and study-specific neurological events. No significant differences were found with respect to efficacy.[47] This favourable safety profile is anticipated to translate to a reduced quality of life burden on patients and a reduced cost burden for the NHS compared with axi-cel
- The introduction of liso-cel to the treatment pathway would make 2L CAR-T cell therapy available for patients with the FL3B and PMBCL subtypes and address a significant unmet need in LBCL patients, who currently have limited treatment options. Liso-cel would maximise the number of patients who are able to potentially benefit from the efficacy associated with CAR-T therapies and the potential for cure earlier in the treatment pathway

B.1.3.1 Health condition

Disease overview

Non-Hodgkin's lymphoma (NHL) comprises a heterogenous group of cancers that begin in the white blood cells, specifically the lymphocytes.[25, 26] Mature B-cell lymphomas are an aggressive class of NHL, characterised by the development of abnormal, often enlarged B-cells which are unable to function correctly and instead multiply uncontrollably, spreading throughout the body and accumulating in lymph nodes.[48, 49] These abnormal B-cells impair the normal anatomy of the affected lymph node and lack the typical signals required for controlled cell growth and replication.[25]

The category of mature B-cell lymphomas comprises 12 families/classes of lymphomas that are further classified into types and subtypes. Of these, DLBCL not otherwise specified (NOS) (including DLBCL arising from indolent lymphoma), HGBCL with *MYC* and *BCL2* and/or *BCL6* translocations, HGBCL NOS, PMBCL and FL3B (also referred to as follicular large B-cell lymphoma [FLBCL]) are commonly grouped together.[48] Liso-cel is indicated for the treatment of patients with DLBCL, HGBCL, PMBCL or FL3B who are eligible for SCT and who relapsed within 12 months from completion of, or are refractory to, first-line immunochemotherapy. As noted above in Section B.1.1, these four B-cell lymphoma types (DLBCL, PMBCL, FL3B and HGBCL) are the focus of this submission and will be referred to as LBCL hereafter.

An estimated 5,440 people are newly diagnosed with LBCLs each year in the UK, with an annual incidence of 8.3 cases per 100,000 people.[27, 28] More than a third (36%) of all new NHL cases in the UK are diagnosed in people aged 75 and over with a higher incidence in men than women.[50] DLBCL represents the most common type of NHL and LBCL, accounting for around 40% of NHL cases and 90% of all LBCL cases in the UK.[27, 30, 51] PMBCL, FL3B and HGBCL are much less common than DLBCL, accounting for around 2–3%, 1% and 1–2% of global NHL cases, respectively.[31, 32] Although the incidences of PMBCL, FL3B and HGBCL are low relative to DLBCL, they collectively represent a sizable proportion of the patients considered in this submission.

LBCLs are classified according to the World Health Organisation (WHO) guidelines for lymphoid neoplasms, with their most recent updates occurring in 2016 and 2022.[29, 48, 52, 53] A summary of the classification and epidemiology of the DLBCL, HGBCL, PMBCL and FL3B types is provided in Table 3.

Table 3: Classification and summary of LBCL types of interest

Type	Description of LBCL type
DLBCL	• DLBCL is the most common type of LBCL and NHL, accounting for around 40% of NHL cases and 90% of all LBCL cases in the UK, with an estimated incidence of 7.4 cases per 100,000 individuals (based on diagnoses between 2010 and 2019)[27, 30, 51] • DLBCL is characterised by an aggressive clinical course with heterogeneity in clinical, pathological and molecular presentation; this can result in varying prognoses for different patients[54] • DLBCL is generally composed of large neoplastic (abnormally growing) B lymphoid cells that express CD19, CD20, CD22, CD79a antigens and

	tends to present in older adult patients, with peak incidence in patients aged 65 – 74 years[35, 55] • In most cases, the causes of DLBCL are unknown[56]
PMBCL	• PMBCL is less common than DLBCL, accounting for 2–3% of NHL cases and 10% of LBCLs.[31] The estimated incidence in the UK is 0.2 cases per 100,000 individuals[30] • Unlike DLBCL, PMBCL also expresses CD30, CD23, PDL1 and PDL2 in addition to CD19/20, giving PMBCL a distinct phenotype compared with DLBCL[35] • PMBCL typically develops within the mediastinal area (the area separating the lungs) and mainly affects young adults (25–40 years) and women.[57, 58] Patients therefore often present with cough, tachypnoea, vein thrombosis, chest pain and dysphagia[33, 59] • Generally, PMBCLs are fast-growing tumours that may also invade adjacent thoracic structures including the chest wall, pleura, lungs, pericardium and heart leading to pleural or pericardial effusion (escape of fluid) in 30–50% of patients[58]
FL3B	• FL3B is a rare subtype of follicular lymphoma (FL).[60] FL is the most common type of low-grade NHL, accounting for approximately 22% of all NHLs, with roughly 2,200 people diagnosed with the disease each year in the UK. Of these cases, approximately 5–10% are classified as FL3B,[61, 62] accounting for around 1% of all NHL cases[31] • Although distinct from DLBCL, because FL3B originates from FL, many aspects of FL3B are similar to DLBCL, including clinical presentation[63, 64] • FL3B was renamed Follicular Large B-cell Lymphoma (FLBCL) in the WHO 2022 classification; however, the FLBCL type is largely in line with the 2008/2016 classification of FL3B, and renaming was done to achieve consistency throughout the classification[48]
HGBCL	• HGBCL is the classification given to a group of aggressive lymphomas, categorised by the presence of changes called translocations of certain genes. Data on the incidence of HGBCL are limited, but it is generally considered a rare subtype, with one study reporting that HGBCLs represent 1–2 % of NHLs[32] • In <10% of DLBCL cases, a regulator gene called *MYC* that modulates cell proliferation, differentiation and survival is expressed. In approximately half of these cases expressing *MYC,* a *BLC2* and/or *BCL6* translocation (which are genes regulating apoptosis) can also occur[65, 66] • These are referred to as double (if both *MYC* and either *BLC2* or *BCL6* are rearranged) or triple (if all 3 rearrangements are observed)-hit lymphomas and are collectively classified as HGBCL[65, 66] • HGBCL commonly presents in elderly patients, with widespread disease found in both the lymph nodes and extranodal regions. Patients often present with elevated lactate dehydrogenase (LDH), high International Prognostic Index (IPI) score, as well as bone marrow and central nervous system (CNS) involvement[33]

Abbreviations: CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; FL3B: follicular lymphoma grade 3B; FLBCL: Follicular Large B-cell Lymphoma; HGBCL: high-grade B-cell lymphoma; IPI: International Prognostic Index; LDH: lactate dehydrogenase; N/A: not applicable; NHL: Non-Hodgkin lymphoma; PMBCL: primary mediastinal large B-cell lymphoma.

Risk factors

LBCL, regardless of type, is the result of both genetic and environmental factors.[67] Key non-modifiable risk factors include advanced age and male gender, a genetic susceptibility or family history, race or ethnicity, viral infections (e.g. human immunodeficiency virus [HIV]) and B-cell activating autoimmune disorders (e.g. systemic lupus erythematous [SLE]).[35, 68-71] Key modifiable risk factors in LBCL include long-term environmental or occupational exposures to chemicals such as pesticides or residues (e.g. glyphosate, malathion or diazinon) and excess adiposity (especially during young adulthood).[68, 70, 72-74]

Diagnosis and staging

The diagnostic process for LBCL is comprised of a complete physical exam including screening for B symptoms (such as fever, night sweats and weight loss), laboratory testing and assessing the size of the liver and spleen.[33] The diagnosis of LBCL is confirmed through an excisional biopsy (surgical procedure removing the tumour), if feasible, of an enlarged lymph node considered to be cancerous based on clinical examination and radiographic imaging.[35] A needle-core biopsy (medical procedure removing a small sample of tissue) is a suitable alternative if surgery is impractical or entails excessive risk.[75] A positron emission tomography and computed tomography (PET/CT) scan is recommended for staging and may also be used to visualise the sites of disease, including extranodal sites, and to determine the preferred site of biopsy.[26, 75-77] Once the biopsy is obtained, cytomorphology and subclassification is ascertained by immunohistochemistry (IHC) and/or flow cytometry (laboratory techniques used to detect antigens on the surface of cancer cells).[27, 76] Cytogenetic fluorescence in situ hybridisation (FISH) testing (used to visualise the genetic material of cancer cells) may also be carried out to determine whether *MYC*, *BCL2*, and/or *BCL6* rearrangements are present.[75, 78, 79]

LBCLs can be staged using the Lugano classification, which was developed by the Lugano Classification Committee in 2014, or the Ann Arbor staging system.[77, 80] Both staging systems are similar and categorise the disease in four stages based on the location and extent of disease, as summarised in Table 4.

Table 4: Summary of the Lugano classification and Ann Arbor staging system

Disease stage	Lugano classification	Ann Arbor staging system
Stage I	Disease involvement in a single node or group of adjacent nodes	Involvement confined to a single lymph node region or single extranodal site
Stage II	Disease involvement in two or more lymph nodes on the same side of the diaphragm	Involvement of more than one lymph node on one side of the diaphragm with or without limited contiguous extranodal involvement
Stage III	Disease involvement in lymph nodes on both sides of the diaphragm	
Stage IV	Diffuse or disseminated disease involvement of one or more extranodal organs or tissues with or without associated lymph node involvement	Diffuse or extensive extranodal involvement, with or without nodal involvement

Sources: Chesson et al. (2014);[80] El-Galaly et al. (2018).[77]

Prognostic factors for LBCL

Several prognostic factors for LBCL have been shown to be independently associated with patient outcomes. Primary scoring systems assessing clinical parameters may be used to determine prognosis and risk adapt the treatment strategy.[81] The International Prognostic Index (IPI), revised IPI (R-IPI), National Comprehensive Cancer Network-IPI (NCCN-IPI), age-adjusted IPI (aaIPI) and secondary aaIPI (sAAIPI) scoring systems all incorporate clinical parameters prognostic for OS including patient age, lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status (PS), disease stage, extranodal involvement and Karnofsky PS (KPS) to estimate patient prognosis.[33, 35, 82, 83] The sAAIPI has been evaluated as a predictor of progression-free survival (PFS) and overall survival (OS) in a retrospective cohort study of 150 patients with aggressive R/R DLBCL who were eligible for SCT. The study found the sAAIPI accurately identified three risk groups with different PFS and OS based on presence of prognostic factors; low risk (0 factors), 70% and 74%; intermediate risk (1 factor), 39% and 49%; and high risk (2 or 3 factors), 16% and 18% (P <0.001 for both PFS and OS, respectively).[83] This highlights the importance of prognostic factors and predictive tools that can aid physicians through the treatment decision-making process.

Patients with R/R LBCL have either experienced disease progression following a period of remission (relapse) or have not responded to treatment (i.e. experienced a best response of either stable disease or worse) (refractory). For patients with R/R LBCL, timing of relapse following first-line (1L) therapy, and therefore the status of lymphoma at the time of receiving re-induction therapy for 2L treatment, is also a key prognostic factor for patient outcomes. Thus, patients with early relapsed/primary refractory LBCL have reduced response rates to 2L treatment and reduced survival rates, which has been highlighted in several DLBCL studies, as presented in Section B.1.3.2.

B.1.3.2 Clinical outcomes

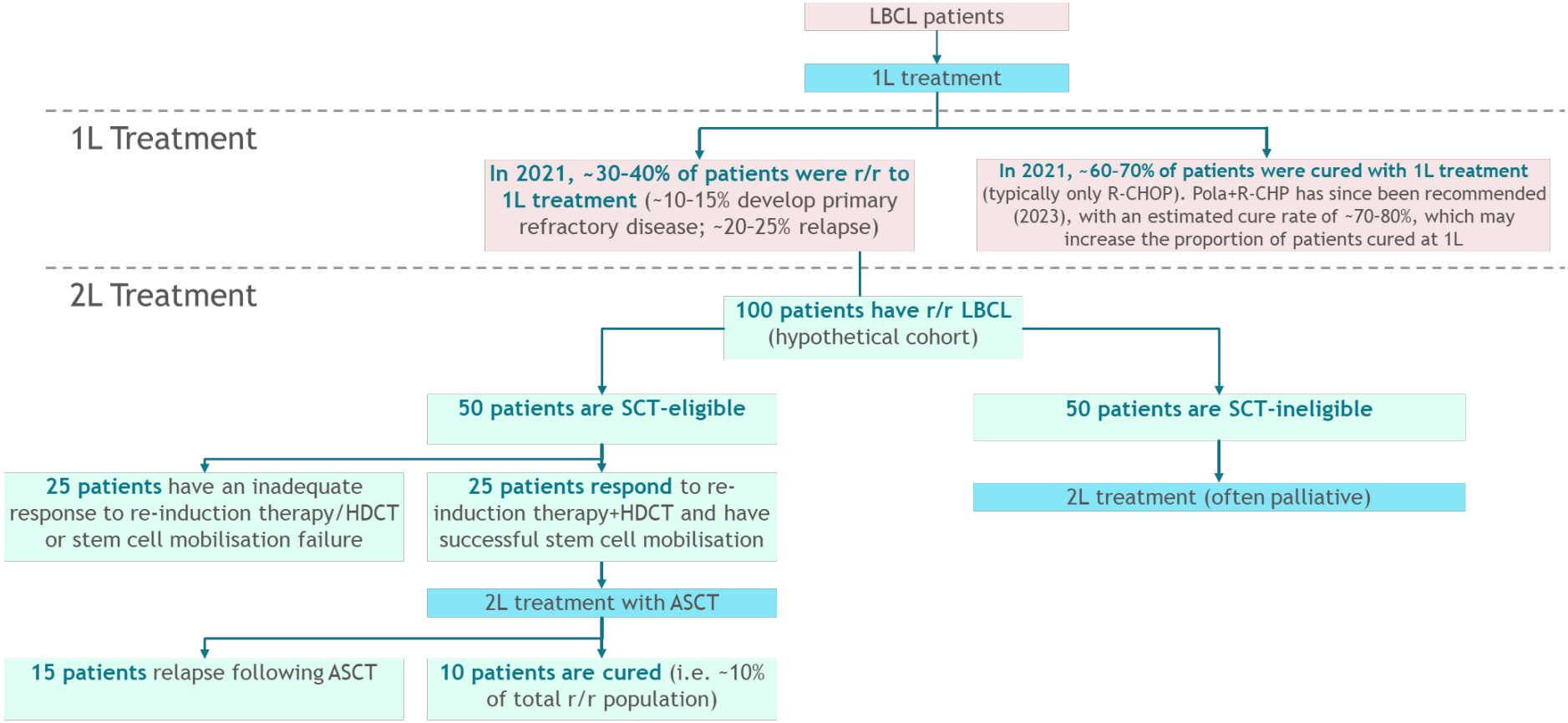
Data on LBCL as a whole and the rarer types of LBCL, including PMBCL, HGBCL and FL3B are limited. Due to limited data across the rarer subtypes of LBCL, the following sections primarily focus on data for DLBCL. UK clinical experts agreed that data for DLBCL is generalisable to PMBCL, HGBCL and FL3B due to similar disease characteristics, treatment pathway and clinical outcomes at the second-line treatment setting.[45]

LBCL is a curable disease; in 2021, it was estimated that approximately 60–70% of patients would be cured after receiving 1L R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone].[34, 35] However, despite the curative intent of 1L treatment, approximately 30-40% of patients will not achieve cure at 1L. Of those who do not achieve cure, an estimated 10–15% of LBCL patients develop primary refractory disease and the remaining 20–25% of patients will relapse after an initial response to 1L treatment.[34, 35] Since these findings polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, prednisolone (Pola+R-CHP) has been recommended by NICE in 2023 for use in patients with untreated DLBCL (TA874).[84] With an estimated cure rate of 70–80%, Pola+R-CHP may increase the total proportion of patients cured at 1L following its uptake in UK clinical practice.[84] According to UK clinical experts, Pola+BR usage at 2L is now rare. This is because most patients would have already received polatuzumab in the 1L setting following the 2023 NICE recommendation of Pola+R-CHP for the treatment of patients with DLBCL (TA874).[45, 84]

For patients who are early relapsed/primary refractory to 1L treatment, the only potentially curative 2L treatment option available via routine commissioning in the UK is re-induction immunochemotherapy followed by HDCT and ASCT. Approximately 50% of patients with early relapsed/primary refractory LBCL are ineligible for SCT (due to advanced age, poor performance status and/or organ dysfunction) and for these patients there is no established SOC and treatment is often palliative.[35, 38, 85] In addition, only around 50% of patients intended for transplant go onto receive ASCT for reasons including, but not limited to, inadequate response to re-induction therapy or stem cell mobilisation failure (pre-transplantation stem cell mobilisation is required for stem cell harvesting, which is a precursor to ASCT).[40] For patients who are eligible for SCT, the timing of relapse after 1L therapy is a strong determinant of receipt of ASCT, with early relapse/primary refractory patients less likely to respond to re-induction therapy and therefore be eligible to receive ASCT (discussed in further detail below).[39, 40, 86]

For those patients who are eligible for SCT and do receive ASCT, there is no guarantee of a cure, with approximately half of early relapsed/primary refractory DLBCL patients treated with ASCT experiencing further relapse.[33, 36, 37, 39, 40, 86] As a result, the outcomes for patients with early relapsed/primary refractory LBCL who are eligible for SCT are poor and only an estimated 10% of patients will be cured with current 2L SOC, as depicted in Figure 3.[38] UK clinical experts agreed that the data presented in Figure 3 is representative of the UK clinical treatment pathway. The experts highlighted that patients relapsing within 12 months have poor clinical outcomes with SCT, which is considered toxic and ineffective for patients.[45]

Figure 3: Estimated cure rates with routinely available treatments for LBCL[a]



Footnotes: [a] All data presented are based on the broader R/R population and it is anticipated that fewer numbers of patients would proceed to ASCT in the early relapsed/primary refractory population.

Abbreviations: 1L: first-line; 2L: second-line; ASCT: autologous stem cell transplant; EFS: event-free survival; HDCT: high-dose chemotherapy; LBCL: large B-cell lymphoma; OS: overall survival; Pola+R-CHP: polatuzumab vedotin, rituximab, doxorubicin, cyclophosphamide, prednisolone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R/R: relapsed or refractory; SCT: stem cell transplant; SoC: standard of care.

Sources: Friedberg et al. (2011);[38] Sehn and Salles et al. (2021);[35]; NICE TA874;[84]; BMS Data on File: TRANSFORM CSR (Final DCO; October 2023).[41]

Early relapsed/primary refractory clinical burden

The clinical burden is particularly high among early relapsed/primary refractory LBCL patients, who are the focus of this submission. Patients who are eligible for SCT presenting with an early relapse (≤12 months following 1L therapy) have a lower overall response rate (ORR) to re-induction immunochemotherapy and a shorter median progression-free survival (PFS) compared with patients relapsing >12 months after 1L therapy.[40] In the ORCHARRD study, which included patients with early relapsed/primary refractory DLBCL who were eligible for SCT (n=316), patients experiencing early relapse exhibited an ORR of 29% and median PFS of 2 months. In contrast, those who relapsed > 12 months after their 1L therapy demonstrated a higher ORR of 67% and a longer median PFS of 24 months.[40] This resulted in fewer SCT eligible patients who relapsed early receiving ASCT in the 2L setting compared with patients who relapsed later (26% versus 59%).[40]

Furthermore, a reduction in the number of patients receiving ASCT translates into poorer overall outcomes for this group presenting with early relapses. This was demonstrated in the CORAL study in a subgroup of patients with early relapsed/primary refractory DLBCL (n=187). In this study patients with early relapse had lower three-year OS rates (39%) compared with patients who relapsed >12 months after 1L therapy (64%), highlighting the significant unmet need of the early relapsed/primary refractory LBCL patients considered in this submission.[39]

The limited efficacy of current UK 2L treatment options for early relapse/primary refractory patients has been further highlighted in the TRANSFORM, ZUMA-7, CORAL and ORCHARRD trials, as presented below in Table 5. Median EFS and two- or three-year EFS were similar across studies. OS differed between studies in terms of median OS (9 months in ORCHARRD versus 35.1 months in ZUMA-7) as well as two-year OS rate (31% in ORCHARRD compared to 58.2% in TRANSFORM). This is likely due to OS being influenced by the availability of subsequent treatments; in TRANSFORM and ZUMA-7, patients could receive subsequent CAR-T therapy which likely increased the OS compared with the older ORCHARRD study, where CAR-T was not available as a subsequent therapy.

Table 5: Patient outcomes with current 2L SOC treatment for early relapse/primary refractory LBCL patients

Study	Patient population	EFS	OS
TRANSFORM (2023)[41]	• Adult patients with LBCL eligible for SCT who were early relapsed/primary refractory in the SOC arm (re-induction therapy followed by HDCT and ASCT) (n=92) • SOC arm included 63% DLBCL patients, 22.8% HGBCL patients and 9.8% PMBCL patients	• Median EFS: 2.4 months • EFS rates: [redacted] at two-years and 19.1% at three-years	• Median OS: NE • Two-year OS rate: [redacted]

ZUMA-7 (2022)[5]	SOC arm (re-induction therapy followed by HDCT and ASCT) for patients who were early relapsed/primary refractory (n=197)	• Median EFS: 2.0 months • Two-year EFS rate: 16%	• Median OS 35.1 months • OS rate: NR
CORAL (2010)[36, 39]	Subgroup of patients with primary refractory or early relapse DLBCL who had received 1L therapy (n=187)	• Median EFS: NR • EFS rates: approximately 16% at two-years and 13% at three-years	• Median OS and OS rate: NR
ORCHARRD (2017)[40]	Subgroup of patients with primary refractory or early relapse DLBCL who had received 1L therapy and were eligible for SCT (n=316)	• Median EFS and EFS rate NR	• Median OS was <1 year (approximately 9 months) • Two-year OS rate 31%

Abbreviations: 1L: first-line; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; EFS: event-free survival; HDCT: high-dose chemotherapy; LBCL: large B-cell lymphoma; NE: not evaluable; NR: not reported; OS: overall survival; SCT: stem cell transplant; SOC: standard of care.
Sources: BMS Data on File: TARNSFORM CSR (Final DCO; October 2023);[41] NICE TA895;[5] Gisselbrecht (2010);[39] van Imhoff (2017).[40]

These data further highlight the poor clinical outcomes associated with current 2L therapies for early relapsed/primary refractory LBCL patients and the need for new transformative therapies to improve survival rates and prevent relapses.[39]

B.1.3.3 Burden of disease

Symptom burden

LBCLs typically first present as one or more painless swellings, typically in a lymph node in the neck, groin or abdomen. Patients may also present with B symptoms, which include fever, night sweats and weight loss of more than 10% over a period of six months, which result from the accumulation of abnormal B cells in lymph nodes leading to rapidly enlarging lymphadenopathy (swelling of lymph nodes).[26]

Quality of life impact

Compared to the general population, the health-related quality of life (HRQoL) of patients with LBCL is considerably impaired by the symptoms of the disease, the psychological burden of receiving a cancer diagnosis and the side effects of the available treatments.[42, 43] In a Dutch study using population-based registry data, patients with DLBCL displayed a significantly reduced HRQoL as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) compared with an age- and sex-matched reference cohort of the general population. Statistically significant reductions in HRQoL were observed across all domains, including physical functioning, emotional functioning, cognitive functioning, social functioning, and global quality of life (QoL; all $P < 0.05$).[87]

The current 2L SOC of re-induction therapy followed by HDCT and ASCT is also associated with considerable impact on HRQoL; patients eligible for SCT receiving the current 2L SOC have also

been shown to have significantly reduced long-term HRQoL compared to the general population. A retrospective study of long-term survivors after ASCT conducted in Germany investigating HRQoL using the EORTC QLQ-C30 questionnaire (n=304) showed that global health status did not return to general population levels until 4 years post-transplant.[88] Emotional, physical, role, social and cognitive functions were also all shown to be negatively impacted over the long term.[88]

In addition, patients receiving ASCT are at risk of several short- and long-term side effects, including infection, cardiac or pulmonary toxicity, anaemia and subsequent tumours (as a result of administration of HDCT prior to ASCT, which can damage bone marrow DNA). Late side effects, such as subsequent tumours, are reported in around 10% of patients and can be fatal.[89, 90] A cross-sectional study of 271 lymphoma survivors treated with HDCT followed by ASCT in Norway between 1987 and 2008 found, with a median of follow-up of 8 years after ASCT, 98% of survivors had at least one moderate or more severe late effect and 56% had severe or life-threatening late effects. The survivors had significantly poorer physical and mental HRQoL assessed by the SF-36 compared with age- and sex-matched controls.[44] The significance of late side effects has also been emphasised in a retrospective long-term follow-up of R/R DLBCL patients undergoing ASCT in a US haematology clinical trial (n=309), while relapse was initially the more likely cause of death, non-relapse mortality become the major cause of death after 8 years.[91]

The emotional burden associated with a diagnosis of DLBCL is exacerbated for patients who experience treatment inefficacy, such as those with R/R disease.[92] Patients with R/R LBCL have particularly poor HRQoL starting in the 2L setting and continuing/worsening in the 3L+setting. A systematic literature review (SLR) of current SOC treatments (rituximab, platinum-containing chemotherapy regimens, ASCT and HDCT) on the HRQoL of patients with R/R DLBCL showed that patients have reduced HRQoL and utility while receiving these treatments. The SLR also showed that patients had a 0.22 reduction in health utility when receiving 3L treatments in the early post-ASCT stage in comparison to 2L, suggesting that utility worsens with treatment line.[93] Preventing progression to a later line of treatment is vital to improve HRQoL and bring confidence to patients, caregivers and families knowing that they have an improved likelihood of remaining free of cancer for longer. There is an unmet need for new treatment options for 2L patients to provide hope for patients who experience treatment inefficacy and prevent progression to later lines of treatment.

Economic burden

Management of LBCLs is resource intensive; significant direct costs are incurred related to inpatients visits, emergency visits, General Practitioner (GP) visits, radiation/immunochemotherapy and supportive care visits and outpatient pharmacy prescriptions.[94-97] Notably, healthcare resource utilisation among patients with DLBCL is particularly high in the first year after initial diagnosis and in the 2L setting among patients with R/R disease.[96, 98] A 2017 simulation model of the full DLBCL treatment pathway estimated the total NHS cost burden to be £88–£92 million for new and existing DLBCL patients, roughly one sixth of the annual UK expenditure on haematological disease altogether.[99]

The introduction of a CAR-T therapy at 2L could help alleviate this large economic burden. A Swiss study conducted in patients eligible for SCT compared resource use (excluding severe

complications) for 3L+ CAR-T therapy versus HDCT and ASCT for patients with R/R B-cell lymphoma treated in hospital in 2020. Compared with ASCT, CAR-T therapy required approximately 30% less staff time due to fewer chemotherapy cycles, fewer outpatient visits and shorter hospital stays. Although production costs were approximately eight times higher for CAR-T therapy than for ASCT, the overall treatment time was shorter (30 versus 48 days) and direct labour and overhead costs were 40% and 10% lower, respectively, for CAR-T therapy.[100]

Similarly, in a Chinese study which compared outcomes in patients with R/R NHL who received CAR-T therapy with that of patients who received ASCT, a lower incidence of ≥ grade 3 treatment-related adverse events (SAEs) was reported in patients who received CAR-T therapy (20.7%) compared with those who received ASCT (48.1%).[101] The lower incidence of severe AEs in patients receiving CAR-T therapy is anticipated to translate to lower resource use and costs associated with AE management.

The introduction of an effective CAR-T therapy at 2L which minimises the resource use for LBCL patients would benefit not only patients, but may also reduce the substantial financial burden that LBCL currently imparts on the NHS and UK economy.

B.1.3.4 Current UK treatment pathway

The clinical guidelines for LBCL informing UK clinical practice are from the British Society of Haematology (2023), European Society for Medical Oncology (2015), the NCCN 2023 B-cell Lymphomas guideline and NICE recommendations.[27, 46, 102-106] Despite being recognised as distinct disease types, DLBCL, PMBCL, HGBCL and FL3B are all aggressive forms of LBCL and clinical treatment guidelines from the NCCN recommend they be managed using the same clinical pathway.[33] This is generally the case in UK clinical practice, although some treatment options are only reimbursed for specific LBCL types.[5]

The typical UK treatment pathway for LBCL is presented in Figure 4 and summarised below, based on recent clinical guidelines and published NICE evaluations.[46,27, 33]

First-line treatment

Treatment for 1L LBCL generally involves rituximab-containing immunochemotherapy regimens, which are given with curative intent. Before 2023, the most common regimen used in UK clinical practice was R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), which around 80% of DLBCL patients received in 2015.[33, 107] However, since this data was published, Pola+R-CHP has received a positive recommendation from NICE in 2023 for the treatment of patients with DLBCL (TA874) which may reduce the proportion of patients being treated with R-CHOP in UK clinical practice.[84] According to UK clinical experts, the majority of patients receive Pola-R-CHP in this setting.[45]

Second-line treatment

The population considered in this submission is adult patients with early relapse/primary refractory LBCL who are eligible for SCT, therefore the 2L UK treatment pathway discussed below is focused only on patients who are eligible for SCT. Current SOC for 2L treatment of patients eligible for SCT with early relapsed/primary refractory LBCL is platinum-based re-induction immunochemotherapy and subsequent HDCT and ASCT in responding patients to consolidate their response. Preferred re-induction regimens prior to HDCT and ASCT according to UK clinical experts include R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide), with R-GDP being the most commonly used. As discussed in Section B.1.3.2, of the approximately 50% of early relapsed/primary refractory DLBCL patients considered fit enough for HDCT and ASCT (i.e. patients eligible for SCT), only around half actually go on to receive ASCT.[35-37] Even for patients who do receive ASCT, there is no guarantee of a cure, with approximately half of patients treated with ASCT experiencing further relapse.[36, 37]

At 2L, early relapsed/primary refractory patients eligible for SCT may receive axi-cel via the Cancer Drugs Fund (CDF); however, this does not represent routine clinical practice, and is only available for patients with DLBCL or HGBCL.[5] Outside of the UK, the use of 2L CAR-T therapy, including liso-cel, has recently begun to be recommended in clinical guidelines. The NCCN guidelines were recently updated to include liso-cel and axi-cel for eligible patients with relapsed disease (≤12 months) or primary refractory disease. The NCCN has recognised the transformative outcomes of CAR-T therapies and no longer recommends 2L ASCT in patients with early relapse or primary refractory disease, strongly suggesting that liso-cel may also address the current unmet need of this patient population in the UK.[33]

Third-line treatment

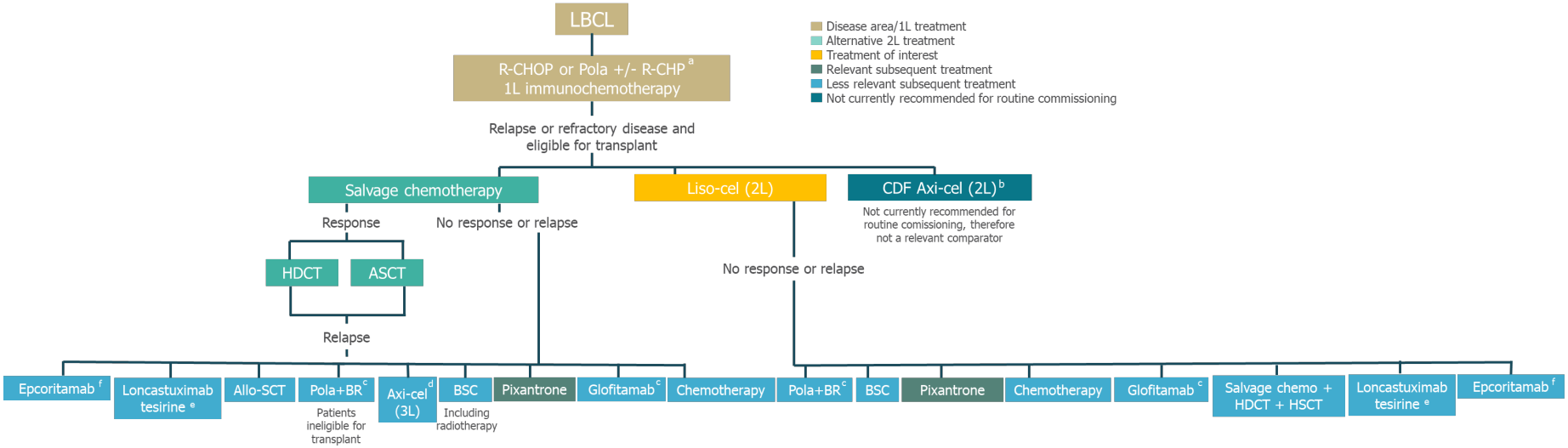
Subsequent treatments in the UK for patients who relapse after ASCT or who are R/R to re-induction immunochemotherapy prior to ASCT include axi-cel, bispecific antibodies (such as glofitamab, and epcoritamab), antibody-drug conjugate (loncastuximab tesirine) or chemotherapy.[5] Notably, 3L+ practice is rapidly evolving in the UK, following the recent NICE recommendations for glofitamab (TA927), loncastuximab tesirine (TA947) and epcoritamab (TA954) within the last 12 months.[105, 106]

UK clinicians estimate that an average of 66.25% (40–85%) of SOC patients would receive 3L+ CAR-T therapy with axi-cel, if eligible, with the majority of the remaining patients receiving 3L+ bispecific antibodies (primarily glofitamab and epcoritamab). A small proportion of patients may receive loncastuximab tesirine or polatuzumab vedotin with rituximab and bendamustine (Pola-BR; if not previously treated with polatuzumab) or 3L+ chemotherapy.

UK clinicians expected that patients treated with liso-cel at 2L would primarily receive subsequent treatment with bispecific antibodies at 3L+, with the majority of patients receiving glofitamab (37.5%; range: 25–40%) or epcoritamab (37.5%; range: 25–40%), and smaller numbers of patients receiving loncastuximab tesirine, chemotherapy, radiotherapy, Pola-BR or allogeneic SCT.

A summary of the UK treatment pathway is provided in Figure 4 below.

Figure 4: UK treatment pathway for LBCL and the anticipated positioning of liso-cel



Footnotes: [a] Pola+R-CHP is recommended only in patients with DLBCL (TA874). [b] Axi-cel at 2L is recommended only in patients with DLBCL (TA895). [c] Glofitamab and Pola+BR at 3L are recommended only in patients with DLBCL (TA927 and TA649). [d] Axi-cel at 3L is recommended only in patients with DLBCL or PMBCL (TA872). [e] Loncastuximab tesirine is recommended only in patients with DLBCL or HGBCL who have received polatuzumab and are ineligible for treatment with CAR-T (NICE TA947). [f] Epcoritamab is recommended only in patients with DLBCL (NICE TA954).
Abbreviations: 1L: first-line; 2L: second-line; ASCT: haematopoietic stem cell therapy; Axi-cel: axicabtagene ciloleucel; BSC: best supportive care; CDF: Cancer Drug Fund; DLBCL: diffuse large B-Cell lymphoma; FL3B: follicular lymphoma grade 3B; LBCL: large B-cell lymphoma; HDCT: high-dose chemotherapy; liso-cell: lisocabtagene maraleucel; PMBCL: primary mediastinal B-cell lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; Pola+BR: polatuzumab vedotin, bendamustine, rituximab; Pola+R-CHP: polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone.
Source: NICE TA895;[5] NICE ID4045;[106] NICE TA947;[105] NICE TA927[103]

B.1.3.5 Unmet need in 2L early relapsed/refractory LBCL patients eligible for SCT

Although many patients with LBCL (~70%) may achieve a cure from 1L therapy, a substantial proportion of patients exhibit primary refractory disease or early relapse following 1L therapy meaning there is a sizable proportion of patients addressed by this submission.[35]

Limited survival benefit associated with current treatments

In this difficult-to-treat 2L population, SOC for patients eligible for SCT includes 2L re-induction immunochemotherapy followed by HDCT and ASCT, which is associated with a limited survival benefit for patients for two reasons.

Firstly, only around 50% of early relapsed/primary refractory LBCL patients who are considered fit enough for HDCT and ASCT (i.e. patients eligible for SCT), actually go on to receive ASCT, for various reasons, such as inadequate response to re-induction therapy or stem cell mobilisation failure.[35-37, 40]

Secondly, although ASCT has the potential for cure, approximately half of people with early relapsed/primary refractory LBCL treated with ASCT will experience a further relapse and progress to 3L+ treatment.[36-38] As outlined in Section B.1.3.2, studies reporting outcomes for people with early relapsed/primary refractory LBCL who are eligible for SCT and receiving current SOC, demonstrated patients experience a median EFS of 2.4 months or less, with durable remissions observed in fewer than a quarter of patients (2-year EFS rates for patients treated 2L SOC ranges from [redacted]).[5, 40, 41] This highlights the current poor clinical outcomes associated with 2L therapies for patients with early relapsed/primary refractory LBCL and the need for new transformative therapies to improve survival rates and prevent relapses.

Toxicity and HRQoL burden of ASCT and further chemotherapy

Those who do receive ASCT are also at risk of persistent and late side effects that can negatively impact long-term QoL.[88, 90] Patients can experience severe side effects from both the HDCT pre ASCT and the reinduction immunochemotherapy regimens. Short-term side effects of ASCT can include infection, anaemia, diarrhoea, fatigue and pneumonitis which can reduce QoL.[90] In addition, longer-term side effects can include subsequent tumours as well as non-malignant late effects including neurosensory, endocrine and cardiopulmonary impairments.[89] As described in Section B.1.3.3, patients receiving the current SOC for early relapsed/primary refractory DLBCL have reduced HRQoL and utility whilst receiving treatment.[93] In addition, long-term survivors of ASCT have been shown to have significantly poorer physical and mental HRQoL compared to age- and sex-matched controls.[44] While CAR-T therapy is also associated with short-term toxicity and lacks a well-established long-term safety profile, its safety profile is comparable to that of the SOC while demonstrating superior efficacy. This increased efficacy consequently enhances patient QoL.[4, 41]

ASCT has been the established 2L SOC for more than 20 years and there is a clear unmet need for new, more effective 2L treatment options for patients with early relapsed/primary refractory LBCL that can induce high response rates and meaningfully extend survival outcome thus reducing the need for subsequent therapies and further declines in patient QoL.

CAR-T Therapies

Liso-cel is a CAR-T therapy anticipated to be licensed for [redacted]

CAR-T cell therapy is an alternative, potentially curative, treatment option for patients with early relapsed/primary refractory LBCL. It is currently only routinely available at the third- or later-line setting in UK clinical practice and has transformed the outcomes for the third line treatment landscape and beyond (3L+).t. However, a considerable proportion of patients will die before reaching later lines of therapy, with overall survival rates varying from 18.5% to 45.5% among patients with early relapsed/primary refractory LBCL, surveyed as part of a multi-centre observational study.[108] Patients that do progress to 3L+ have already received two intensive lines of treatment with suboptimal response and may not be fit enough (or willing) to receive another. The introduction of routinely available CAR-T therapy earlier in the pathway will provide access to CAR-T therapy for patients who may have never have been able to receive this treatment at 3L+. Furthermore, by providing this effective treatment to patients with lower tumour burden, fewer comorbidities and higher fitness levels, the use of CAR-T therapy at 2L may also further improve outcomes compared with 3L and avoid NHS England incurring costs of both 2L ASCT and 3L+ CAR-T therapy.

In the TRANSFORM trial (see Section B.2.6), treatment with liso-cel resulted in a statistically significant and clinically meaningful improvement in EFS compared with SOC, with a median EFS of 29.5 months in the liso-cel arm compared with 2.4 months in the SOC arm (stratified hazard ratio [HR]: 0.375; 95% confidence interval [CI]: 0.259, 0.542). Liso-cel was also associated with statistically significant and clinically meaningful improvements compared with SOC in key secondary endpoints. Complete response rate was 73.9% for liso-cel versus 43.5% for SOC and median PFS was not evaluable (NE) for liso-cel versus 6.2 months for SOC (stratified HR: 0.422; 95% CI: 0.279, 0.639). Median OS was NE for liso-cel and SOC; fewer OS events occurred in the liso-cel arm (32 [37.0%]) versus the SOC arm (42 [45.7%]) (HR: 0.757; 95% CI: 0.481, 1.191).[4] The stratified OS HR of indicates that liso-cel reduces the hazard of death by 24% when compared to SOC. This difference was not statistically significant, but is confounded by the high proportion (66.3%) of SOC patients who crossed over to receive liso-cel as a subsequent treatment in TRANSFORM.[41] These survival results represent a truly clinically meaningful benefit for patients receiving liso-cel over the current SOC of re-induction therapy followed by HDCT and ASCT.

One CAR-T therapy, axi-cel, is available via the CDF for early relapsed/refractory patients who are eligible for SCT at 2L (TA895).[5] This means axi-cel is only funded on an interim basis, and therefore does not represent routine clinical practice. Furthermore, axi-cel is only available for patients with DLBCL or HGBCL, meaning patients with PMBCL and FL3B cannot access a 2L CAR-T cell therapy. For early relapsed/primary refractory PMBCL and FL3B patients, 2L treatment is currently limited to re-induction immunochemotherapy and subsequent HDCT and ASCT; liso-cel is therefore expected to substantially improve outcomes for these patients.

Axi-cel is also associated with a less favourable safety profile compared with liso-cel. The results of a matching-adjusted indirect comparison (MAIC) between liso-cel and axi-cel, which adjusted for clinically meaningful differences between the TRANSFORM and ZUMA-7 trials, found the MAIC-weighted safety outcomes favoured liso-cel, with lower odds of key CAR-T cell-associated

adverse events (AEs) with liso-cel vs axi-cel: cytokine release syndrome (CRS) any grade (odds ratio [OR], 0.09; 95% CI: 0.04–0.19), CRS grade ≥ 3 (OR: 0.10; 95% CI: 0.01, 0.81), neurological events (NE) any grade (OR: 0.10; 95% CI: 0.04, 0.22), and NEs grade ≥ 3 (OR: 0.21, 95% CI: 0.06, 0.69).[109] The MAIC also demonstrated no differences in efficacy outcomes, with median EFS of 10.1 months (95 CI: 6.1, NR) for liso-cel and 8.3 months (95% CI: 4.5, 5.8) for axi-cel, with a HR of 0.94 (95% CI: 0.58, 1.52). Results were consistent for other efficacy parameters of PFS, ORR, and CR rate.

The favourable safety profile of liso-cel compared with axi-cel is expected to reduce the healthcare resource utilisation (HCRU) burden and costs associated with managing CAR-T therapy-specific AEs. For instance, managing CRS grade ≥ 3 was previously estimated to cost £6,900 as part of TA895 based on the cost of tocilizumab and assuming 4 days in the intensive care unit (ICU).[5] Reducing this cost is therefore a significant benefit to the NHS, especially considering the capacity constraints the NHS is currently facing. The more favourable safety profile may additionally increase the potential for outpatient administration of liso-cel, compared to axi-cel which is typically administered as an inpatient treatment. In addition to cost savings, the favourable safety profile for liso-cel is also anticipated to translate to improved QoL for patients. Patients experiencing CRS grade ≥ 3 are typically modelled to have a quality of life of zero, reflecting the severity of this AE which greatly impairs or completely eliminates the patients' ability to lead a normal, functioning life during this period.[110]

Considering the above, a routine, 2L recommendation for liso-cel would represent a significant step change in the current treatment paradigm for patients with early relapsed/refractory LBCL. Liso-cel would address the unmet need and poor prognosis faced by patients who are currently unable to access CAR-T cell therapy until later lines of treatment and maximise the number of patients who are able to potentially benefit from the efficacy associated with CAR-T therapies and the potential for cure earlier in the treatment pathway. For patients who are currently able to access axi-cel via the CDF, liso-cel will provide a routinely available treatment option which is similarly effective and more tolerable, reducing the treatment burden on patient QoL and HCRU for the NHS.

B.1.4 *Equality considerations*

It is not anticipated that the provision (or non-provision) of liso-cel would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Clinical efficacy and safety evidence for liso-cel versus SOC for patients with 2L early relapsed/primary refractory LBCL who are eligible for SCT is provided by the Phase III randomised TRANSFORM trial

- The TRANSFORM trial (NCT03575351) was a global, randomised, open-label, Phase III trial comparing the efficacy and safety of liso-cel versus standard of care (SOC) as a second-line (2L) treatment for patients with early relapsed/primary refractory DLBCL, HGBCL, PMBCL, THRBCL or FL3B (collectively referred to as LBCL) who are eligible for stem cell transplant (SCT)[111]
    - SOC consisted of three cycles of re-induction therapy (R-DHAP, R-ICE or R-GDP) delivered intravenously (IV), followed by high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) in responders. Patients in the SOC arm were eligible to cross over to receive liso-cel following inadequate response or disease progression[4]
- The primary outcome of TRANSFORM was event-free survival (EFS), defined as the time from randomisation to progressive disease, failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomisation, or start of a new antineoplastic therapy due to efficacy concerns or death from any cause, whichever occurs first.[4]
    - EFS is more clinically relevant than progression-free survival (PFS) in this setting, as patients are treated with curative intent. This means stable disease (SD) is not an acceptable outcome and LBCL patients with suboptimal response to treatment will be moved onto a new therapy for potential cure at the earliest opportunity.[5] This was confirmed by UK clinical experts at an advisory board meeting, who agreed EFS was the most relevant endpoint in this indication.[45]
- Secondary outcomes in TRANSFORM included overall response rate (ORR) and CR rate (CRR), overall survival (OS), as well as health-related quality of life (HRQoL) and safety outcomes

Liso-cel increases the number of patients able to receive curative therapy

- Only 46.7% of patients in the SOC arm of TRANSFORM actually received ASCT; the most common reasons for not receiving ASCT were lack of efficacy to re-induction therapy ([redacted]) and disease relapse before receiving HDCT and ASCT ([redacted]). In contrast, treatment with liso-cel was received by 89/92 (96.7%) of patients in the intervention arm of TRANSFORM[41, 112]
- The addition of liso-cel as a 2L treatment option for patients with early relapsed/primary refractory LBCL who are eligible for SCT will increase the number of patients able to receive curative therapy, with almost two times as many patients randomised to the liso-cel arm receiving 2L treatment with curative intent.[41] The use of CAR-T therapy at 2L may also further improve outcomes compared with use at 3L+ and avoid NHS England incurring costs of both 2L ASCT and 3L+ treatments.

Patients treated with liso-cel experienced statistically significant and clinically meaningful improvements in EFS when compared with SOC

- The primary efficacy endpoint of TRANSFORM was met at the March 2021 interim analysis; liso-cel was associated with a statistically significant and clinically meaningful

improvement in EFS versus SOC: the stratified hazard ratio (HR): 0.35 (95% confidence interval [CI]: 0.23, 0.53), p<0.0001[112]

- The superiority of liso-cel versus SOC was confirmed at the time of the final data cut off (DCO) (October 2023):
    - Patients treated with liso-cel experienced a median EFS of 29.5 months, compared with 2.4 months for patients receiving SOC[41]
    - The stratified HR of 0.38 (95% CI: 0.26, 0.54) indicates that liso-cel is associated with a 62% reduction in the risk of experiencing disease progression, death, an inadequate response to treatment, or start of a new antineoplastic therapy versus SOC[41]
    - The 36-month EFS rate for liso-cel was 45.8% (standard error [SE]: [redacted]), versus 19.1% (SE: [redacted]) for SOC[41]

Liso-cel induced a higher response rate and deeper and more durable responses versus SOC

- The CRR for the liso-cel arm was 30.4% higher in the liso-cel arm versus the SOC arm (73.9% [n=68/92] and 43.5% [n=40/92], respectively)[41]
- Similarly, the ORR for the liso-cel arm was 38.1% higher than the SOC arm (87.0% [n=80/92] and 48.9% [n=45/92], respectively).[41]
- Responses to liso-cel were more durable than SOC, with a stratified HR for duration of response (DOR) of 0.60 (95% CI: 0.36, 1.00) (i.e. a 40% reduction in the risk of inadequate response, disease progression or death for patients who initially respond to treatment)[41]
- Median DOR was not evaluable (NE) (95% CI: 16.9, NE) in the liso-cel arm. In the SOC arm the median DOR was 9.1 months (95% CI: 5.1, NE)[41]

Patients treated with liso-cel demonstrated a statistically significant improvement in PFS when compared with SOC

- Liso-cel met the key secondary endpoint of PFS in the primary analysis May 2022 DCO; liso-cel demonstrated a statistically significant improvement in PFS versus SOC: HR: 0.40 (95% CI: 0.26, 0.62); p-value (based on a stratified Cox proportional hazards model [Cox-PH])<0.0001[4]
- The superiority of liso-cel versus SOC was confirmed at the time of the final DCO (October 2023):
    - [redacted] in the liso-cel arm and [redacted] in the SOC arm experienced disease progression or death. Liso-cel was superior to SOC, with a stratified HR of 0.422 (95% CI: 0.28, 0.64)[41]
    - The estimated PFS at 36 months was 50.9% (95% CI: 39.9, 62.0) in the liso-cel arm compared with 26.5% (95% CI: 15.9, 37.1) in the SOC arm[41]
    - Disease progression in the liso-cel and SOC arms occurred in [redacted] of patients, respectively, and death from any cause occurred in [redacted] of patients, respectively[41]

The TRANSFORM trial demonstrates the curative potential of liso-cel for patients who experience the deepest responses to treatment

- With a median follow-up of 33.9 months at the final DCO (October 2023), median OS for liso-cel was not yet estimable. Liso-cel was associated with 2-year and 3-year OS rates of [redacted] and 62.8%, with the OS Kaplan-Meier curve demonstrating a clear plateau from Month 30 onwards[41]
- The stratified OS HR of 0.76 (95% CI: 0.48, 1.19) indicates that liso-cel reduces the hazard of death by 24% when compared to SOC. This difference was not statistically significant, but is confounded by the high proportion (66.3%) of SOC patients who crossed over to receive liso-cel as a subsequent treatment in TRANSFORM[4, 41]
- OS for patients receiving liso-cel is likely underestimated relative to UK clinical practice. UK clinical experts estimated that the majority of patients who are not cured at 2L (64.5%) would receive 3L+ treatment with either glofitamab (TA927) or epcoritamab (TA954) if they required subsequent treatment following liso-cel.[45, 103, 106] In comparison, [redacted] in the TRANSFORM trial after receiving liso-cel; instead, most patients received chemotherapy, which is associated with worse outcomes

Liso-cel delivers clinically meaningful improvements in patient HRQoL versus SOC

- HRQoL was assessed via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – 30 items (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy Lymphoma subscale (FACT-LymS)
- At the IA3 DCO (March 2021), treatment with liso-cel delayed the time to confirmed deterioration in global health status/quality of life (QoL) when compared with SOC (median: NR versus 19.0 weeks, stratified HR: 0.47, 95% CI: 0.24, 0.94)[113]
- Treatment with liso-cel resulted in improvements in HRQoL from baseline over time relative to SOC according to the global health status/QoL, cognitive functioning and fatigue domains of the EORTC QLQ-C30; HRQoL was maintained over time versus SOC in all other domains[41]

Liso-cel is well tolerated; adverse events (AEs) associated with treatment can be well-managed

- Overall, no new safety concerns were identified in patients studied in TRANSFORM and the safety events reported in this study were consistent with the known safety profile of liso-cel
- At the final DCO (October 2023), the number of treatment-emergent adverse events (TEAEs) reported in the liso-cel arm was comparable to the SOC arm; a total of 98.9% of patients in the SOC arm and 100% of patients in the liso-cel arm experienced at least one TEAE during the study and TEAEs of Grade 3/4 occurred in 81 patients (89.0%) who received SOC and 85 patients (92.4%) who received liso-cel[41]
- The rates of CAR-T specific AEs, including cytokine release syndrome (CRS) and neurological toxicity immune effector cell-associated events were relatively low:
    - CRS (any grade) occurred in 45 patients (48.9%) who received liso-cel. Grade 3 CRS occurred in only 1 patient (1.1%) who received liso-cel[41]
    - Neurological toxicity immune effector cell-associated events (any grade) and Grade 3 occurred in 10 patients (10.9%) and 4 patients (4.3%) who received liso-cel, respectively[41]

- No Grade 4/5 CRS or neurological toxicity immune effector cell-associated events were observed in patients treated with liso-cel[41]

- The majority of these AEs were mild to moderate in severity and manageable with protocol-specified guidelines and/or local standards of care[41]

Conclusion

- Liso-cel would provide a routinely available CAR-T therapy for patients with early relapsed/primary refractory disease at 2L that is expected to increase the number of patients receiving curative therapy and provide significant benefit to patients through higher cure rates, superior response and improved survival outcomes compared with current SOC

B.2.1 *Identification and selection of relevant studies*

An SLR was originally conducted in October 2017, and updated in April 2019, to identify any published evidence reporting on the efficacy and safety of current therapies used in the treatment of patients with early relapsed/primary refractory LBCL. In July 2020, the SLR was updated to specifically include patients receiving 2L therapy. The scope of the SLR was narrowed in subsequent updates performed in June 2021, December 2021, March 2023 and February 2024 (the most recent update) to focus on the identification of studies reporting on the efficacy and safety of current therapies used as 2L treatment options in LBCL patients who are eligible for SCT. Overall, the SLR identified 181 relevant publications, reporting on 124 unique studies.

Full details of the SLR methodology used to identify the clinical evidence relevant to liso-cel in this submission, including the search and PICO strategy, preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified one RCT investigating the efficacy and safety of liso-cel for 2L patients with early relapsed/primary refractory LBCL who are eligible for SCT: TRANSFORM (NCT03575351).[111] Data from TRANSFORM are provided in the following sections and the clinical study report (CSR) for the final data-cut off (October 2023 DCO) and earlier March 2022 DCO are located in the reference pack accompanying this submission.[41] An overview of the TRANSFORM trial is presented in Table 6.

Table 6: Clinical effectiveness evidence

Study	**TRANSFORM (NCT03575351)**
Study design	Global, randomised, open-label, multicentre, Phase III trial
Population	Adult patients with LBCL who have relapsed within 12 months, or are primary refractory to 1L immunochemotherapy and are eligible for SCT
Intervention(s)	Lisocabtagene maraleucel (liso-cel; Breyanzi®)

Study	TRANSFORM (NCT03575351)
Comparator(s)	SOC consisted of three cycles of re-induction therapy (R-DHAP, R-ICE or R-GDP) delivered IV followed by HDCT and ASCT in responders
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Reported outcomes specified in the decision problem[a]	• **EFS**
	• **OS**
	• PFS
	• Response to treatment, including:
	  ○ CRR
	  ○ DOR
	  ○ ORR
	• **AEs of treatment**
	• **HRQoL**

All other reported outcomes	**Other secondary endpoints:** PFS on next line of treatment (PFS2), rate of HDCT and ASCT completion, response rate post-ASCT, hospital resource utilisation **Exploratory endpoints:** evaluate the immune responses against liso-cel, assess the efficacy and safety for patients who crossed-over to liso-cel, characterise the pharmacokinetics and pharmacodynamic profile of liso-cel (including B-cell aplasia and soluble biomarkers such as chemokines and cytokines) and evaluate the role of the tumour and the tumour microenvironment in mechanisms of response and resistance to liso-cel

Footnotes: [a] Outcomes marked in bold are included in the economic model.
Abbreviations: AE: advent event; ASCT: autologous stem cell transplant; CRR: complete response rate; DOR: duration of response: EFS: event-free survival; HDCT: high-dose chemotherapy; HRQoL: health-related quality of life; IV: intravenously; LBCL: large B-cell lymphoma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R- GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; SCT: stem cell transplant; SOC: standard of care.
Source: Abramson *et al.* (2023);[4] BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

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

B.2.3.1 Study design

The TRANSFORM trial is a randomised, open-label, parallel-group, multi-centre trial that evaluates the efficacy and safety of liso-cel versus SOC (consisting of three cycles of re-

induction therapy followed by HDCT and ASCT in responders) as a 2L therapy in patients who have early relapsed/primary refractory disease and are eligible for SCT with:

- DLBCL not otherwise specified (NOS), de novo or transformed from indolent NHL
- HGBCL with rearrangements of *MYC* and either *BCL2, BCL6*, or both with DLBCL histology
- PMBCL
- T-cell histiocyte rich LBCL (THRBCL)
- FL3B

The time of relapse was calculated from the date of the first disease assessment confirming a CR obtained with 1L treatment for disease under study, to the date of first assessment demonstrating a relapse.

Randomisation and study treatments

Randomisation was performed using the permuted-blocks method with a dynamic block size (block size of 4 with probability of 0.75 and block size of 6 with probability of 0.25) by an interactive response technology. Randomisation was stratified by response to 1L therapy (refractory (stable disease [SD], progressive disease [PD], partial response [PR] or CR with relapse before 3 months) versus relapse (CR with relapse on or after lasting at least 3 months) and sAAIPI (0–1 versus 2–3).

All patients underwent leukapheresis before being randomly assigned in a 1:1 ratio to either:

- **SOC arm**: re-induction therapy followed by HDCT and ASCT (collectively referred to as SOC)
    - All patients randomised to the SOC arm received three cycles of SOC re-induction therapy followed by HDCT and ASCT. The three permitted re-induction regimens were R-DHAP, R-ICE and R-GDP
    - Patients who responded to re-induction therapy proceeded to one cycle of HDCT and ASCT
    - In the event of toxicity or non-satisfactory response to the selected SOC regimen (as per investigator judgment), a switch within the 3 defined SOC regimens was allowed in order to maximise a patient's chance to receive the full three cycles of re-induction immunochemotherapy before declaring failure of the treatment; this was not considered an EFS event
- **Liso-cel arm**: bridging therapy, if needed, followed by lymphodepleting chemotherapy (LDC) and liso-cel
    - Patients randomised to the liso-cel arm received LDC for 3 days followed by liso-cel as two sequential IV infusions. Patients could receive one cycle of bridging therapy with one of the three defined re-induction immunochemotherapy regimens permitted in the SOC group per investigator discretion during liso-cel manufacturing

Eligibility for cross-over

If requested by the investigator, patients in the SOC arm could receive liso-cel upon central confirmation by the Independent Review Committee (IRC) of one of the following criteria:

- Failure to achieve CR or PR by 9 weeks post-randomisation (after 3 cycles of SOC)
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns (absence of CR) after 18 weeks post-randomisation

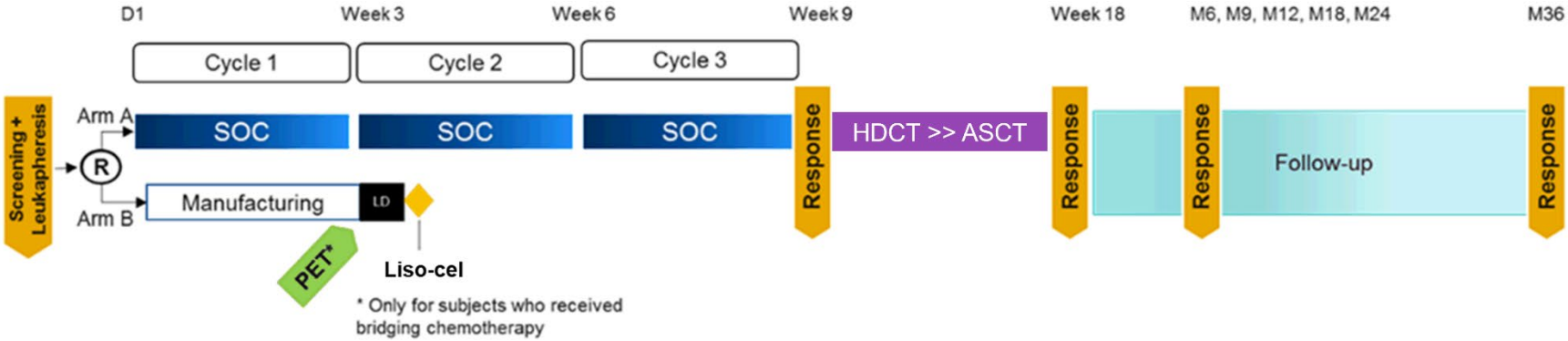
Patients must have met the criteria for LDC as well as for starting liso-cel in addition to confirmation of an EFS event in order to receive liso-cel. All patients underwent leukapheresis before being randomly assigned and liso-cel manufacturing was performed for patients in the liso-cel and SOC arms to enable rapid liso-cel infusion post SOC failure.

Follow-up visits

The first response evaluations were performed at Week 9 (after 3 cycles of SOC or 5 weeks after liso-cel infusion) and Week 18 (8 weeks after the start of HDCT for the SOC arm or 14 weeks after liso-cel infusion). During the post-treatment phase, efficacy and safety follow-up visits were scheduled at Months 6, 9, 12, 18, 24 and 36 (or end of study [EOS]).

A summary of the trial design is illustrated in Figure 5 and an overview of the trial methodology, including the key eligibility criteria for TRANSFORM, is provided in Table 7. The full eligibility criteria are presented in Appendix M.

Figure 5: TRANSFORM study design



Footnotes: For patients in the SOC arm, eligibility criteria for crossover to receive liso-cel was also defined. The criteria included central confirmation by the IRC of one of the following: failure to achieve CR or PR by 9 weeks post-randomisation (after 3 cycles of SOC), progression at any time, or need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomisation. For patients in the liso-cel arm, bridging chemotherapy with one cycle of a SOC regimen was allowed for disease control while liso-cel was being manufactured, if deemed necessary by the investigator. Arm A = SOC arm; Arm B = liso-cel arm
Abbreviations: ASCT: autologous stem cell transplant; CR: complete response; HDCT: high-dose chemotherapy; IRC: Independent Review Committee; liso-cel: lisocabtagene maraleucel; PET: positron emission tomography; PR: partial response; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 7: Key study characteristics for TRANSFORM

(Primary) study objective	To compare the efficacy in patients treated with liso-cel versus patients treated according to SOC, defined as EFS
Study location	The study was conducted at 47 sites in 11 countries: Belgium, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, the United Kingdom, the United States
Trial design	Randomised, open-label, parallel-group, multicentre, Phase III trial
Method of allocation	Patients who met the eligibility criteria were randomised using the permuted-blocks method by an interactive web response system to either liso-cel or SOC in a 1:1 ratio. Randomisation was stratified by: 1. Best ORR to 1L therapy: refractory (defined as SD, PD, PR, or CR with relapse before 3 months) versus relapse (CR with relapse on or after 3 months but no more than 12 months) 2. sAAIPI: 0–1 versus 2–3

Key inclusion criteria	• Aged 18–75 years at the time of signing the informed consent form
	• Eligible for ASCT
	• Relapsed or refractory LBCL
	• ECOG performance status of 1 or less
	• Adequate organ function, defined as:
	  ○ Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.0 x 109 cells/L and platelets ≥ 50 x 109 cells/L in absence of bone marrow involvement
	  ○ Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance > 45 mL/min
	  ○ Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for patients with Gilbert's syndrome or lymphomatous infiltration of the liver)
	  ○ Adequate pulmonary function, defined as ≤ Grade 1 dyspnoea according to Common Terminology Criteria for Adverse Events (CTCAE) and oxygen saturation (SaO2) ≥ 92% on room air and FEV1 ≥ 50%
	  ○ Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) performed within 4 weeks of randomisation
	• PET-positive disease as per Lugano 2014 criteria[80]

Key exclusion criteria	• Patient had any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study based on investigator's judgment • Patient had any condition, including the presence of laboratory abnormalities, which placed the patient at unacceptable risk if he/she were to participate in the study based on investigator´s judgment

	• Patient had any condition that confounded the ability to interpret data from the study based on investigator's judgment • Patients not eligible for ASCT • Patients planned to undergo allogeneic stem cell transplant • Patients with primary cutaneous LBCL, Epstein-Barr virus (EBV) positive DLBCL, Burkitt lymphoma or transformation from chronic lymphocytic leukaemia/small lymphocytic lymphoma (Richter transformation)

Study drugs	**SOC**
	• Patients randomly assigned to the SOC arm received 3 cycles of SOC re-induction therapy followed by HDCT and ASCT. The permitted re-induction regimens were:
	  ○ R-DHAP: rituximab 375 mg/m^2 on Day 1, dexamethasone 40 mg on Days 1 to 4, cytarabine 2 x 2000 mg/m^2 on Day 2 and cisplatin 100 mg/m^2 on Day 1
	  ○ R-ICE: rituximab 375 mg/m^2 on Day 1, ifosfamide 5000 mg/m^2 on Day 2, etoposide 100 mg/m^2 on Days 1 to 3 and carboplatin area under the curve (AUC) 5 (maximum dose 800 mg) on Day 2
	  ○ R-GDP: rituximab 375 mg/m^2 on Day 1, dexamethasone 40 mg on Days 1 to 4, gemcitabine 1000 mg/m^2 on Days 1 and 8 and cisplatin 75 mg/m^2 on Day 1
	• Patients who responded to re-induction therapy proceeded to one cycle of HDCT (IV carmustine 300 mg/m² on day 1, etoposide 200 mg/m² on days 2–5, cytarabine 200 mg/m² on days 2–5, and melphalan 140 mg/m² on day 6) and ASCT
	
	Liso-cel
	• Patients randomised to the liso-cel arm received LDC (IV fludarabine 30 mg/m² and IV cyclophosphamide 300 mg/m² daily) for 3 days followed by liso-cel. Patients received liso-cel as two sequential IV infusions of CD8+ and CD4+ CAR-T cells at a total target dose of 100 × 10^6 CAR-T cells

Permitted and disallowed concomitant medications	**Permitted concomitant medications**: • Use of immunosuppressive medications for the management of investigational product (IP)-related AEs or in patients with contrast allergies was acceptable • Use of inhaled and intranasal corticosteroids was permitted; therapeutic doses of steroids were used in life-threatening situations and for other medical conditions when indicated **Prohibited concomitant medications** • Any investigational antineoplastic therapy • Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment (except intrathecal [IT] prophylaxis and treatment for secondary central nervous system [CNS] involvement)

	• Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable • Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 20 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha (TNF-α) blockers
Primary outcome	EFS
Secondary outcomes[a]	**Key secondary objectives**: • CRR • PFS • OS **Other secondary objectives:** • DOR • ORR • AE • Serious adverse events (SAE) • HRQoL

Pre-specified subgroups	Efficacy subgroup analyses was performed on the following variables:
	• sAAIPI status: 0–1 versus 2–3
	• Prior response status: refractory versus relapse to last prior therapy. The status was refractory if a patient achieved SD, PD, PR or CR with relapse within 3 months to last prior therapy; otherwise, the status was relapsed
	• Age: < 40, ≥ 40 to < 65, ≥ 65 to < 75 and ≥75 years at the time of randomisation
	• Sex: male versus female
	• Ethnicity: Hispanic or Latino versus not Hispanic or Latino
	• Region: Europe, US and Japan
	• Race: white versus other races
	• ECOG performance status at screening: 0 and 1
	• Prior chemotherapy response status: chemorefractory versus chemosensitive to last therapy. The status was chemorefractory if a patient achieved SD or PD to last chemotherapy-containing regimen; otherwise, the status was chemosensitive
	• CNS disease status: CNS disease versus no known CNS disease at the time of randomisation
	• Histological and molecular subtype:
	  ○ NHL type: DLBCL, FL3B, high grade B-cell lymphoma with DLBCL histology, PMBCL or THRBCL
	  ○ DLBCL subtype: DLBCL NOS de novo or DLBCL from transformed indolent NHL
	  ○ DLBCL subtype based on cell of origin: germinal centre B-cell (GCB) or activated B-cell-like (ABC), non-GCB
	• Bridging therapy status: impact of bridging therapy

	treatment effect versus SOC was evaluated in patients receiving bridging Subgroup analyses was only performed if there were enough patients in each subgroup (more than 10 patients in each subgroup).
Duration of study and follow-up	The study lasted approximately 3 years from the time the last patient is randomised. Randomisation of all patients was estimated to take up to 20 months from first patient in. The end of trial is defined as one of the following, whichever is the later date: • The date of the last visit of the last patient to complete the post-treatment follow-up • The date when the last patient enters the long term follow up study • The date of receipt of the last data point from the last patient that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol

Abbreviations: 1L: first line; ABC: activated B-cell; AE: adverse event; ANC: absolute neutrophil count; ALT: alanine aminotransferase; ASCT: autologous stem cell transplant; CNS: central nervous system; CR: complete response; CRR: complete response rate; CTCAE: Common Terminology Criteria for Adverse Events; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; EBV: Epstein-Barr virus; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; FL3B: follicular lymphoma grade 3B; GCB: germinal centre B-cell; HDCT: high-dose chemotherapy; HRQoL: health-related quality of life; IP: investigational product; IT: intrathecal; IV: intravenously; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; MUGA: multi-gated acquisition scan; NHL: non-Hodgkin's lymphoma; NOS: not otherwise specified; ORR: overall response rate; OS: overall survival; PD: progressive disease; PET: positron emission tomography; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; PR: partial response; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; sAAIPI: secondary age-adjusted International Prognostic Index; SAE: serious adverse event; SaO2: oxygen saturation; SCT: stem cell transplant; SD: stable disease; SOC: standard of care; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma; TNF-α: tumour necrosis factor alpha; ULN: upper limit of normal.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023);[41] BMS Data on File: TRANSFORM CSR (May 2022 DCO).[114]

B.2.3.2 Baseline characteristics

Demographic characteristics

The demographic characteristics for the intention-to-treat (ITT) analysis set in the TRANSFORM trial cohort are summarised in Table 8 below. Demographic characteristics for the ITT analysis set were generally balanced between the liso-cel arm and the SOC arm.

The median age was [redacted] years (range: [redacted]) and 105 (57.1%) patients in the trial were male. The majority of patients were white (109 [59.2%]), 18 [9.8%] were Asian and seven (3.8%) were Black or African American. Race was not collected or reported in 47 (25.5%) of patients.[112] The majority of patients had a baseline ECOG performance status of 0–1 (181 [98.4%]), with the remaining patients having a baseline ECOG performance status of 2 (3 [1.6%]).[41]

Generally, UK clinical experts stated that the baseline demographic characteristics of patients in the TRANSFORM trial were aligned with those of patients in UK clinical practice.[45]

Table 8: Key demographic characteristics

Number of treated patients, n (%)	SOC Arm (n=92)	Liso-cel Arm (n=92)	Total (N=184)
Age (years)			
Median (range: min, max)	58.0 (26, 75)	60.0 (20, 74)	[redacted]
Age category (years)			
<65 years	67 (72.8)	56 (60.9)	123 (66.8)
≥65 to <75 years	23 (25.0)	36 (39.1)	59 (32.1)
≥75 years	2 (2.2)	0	2 (1.1)
Sex (at birth)			
Male	61 (66.3)	44 (47.8)	105 (57.1)
Female	31 (33.7)	48 (52.2)	79 (42.9)
Race			
White	55 (59.8)	54 (58.7)	109 (59.2)
Asian	8 (8.7)	10 (10.9)	18 (9.8)
Black or African American	3 (3.3)	4 (4.3)	7 (3.8)
Not reported	25 (27.2)	22 (23.9)	47 (25.5)
Ethnicity			
Hispanic or Latino	3 (3.3)	3 (3.3)	6 (3.3)
Not Hispanic or Latino	62 (67.4)	65 (70.7)	127 (69.0)
Not reported	26 (28.3)	24 (26.1)	50 (27.2)
Unknown	1 (1.1)	0	1 (0.5)
ECOG performance status at screening			
0	57 (62.0)	48 (52.2)	105 (57.1)
1	35 (38.0)	44 (47.8)	79 (42.9)
ECOG performance status at baseline			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Hematopoietic cell transplantation-specific comorbidity index			
N	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Left ventricular ejection fraction result			
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Viral serology			
Hepatitis B virus surface antigen			
Negative	[redacted]	[redacted]	[redacted]
Positive	[redacted]	[redacted]	[redacted]
Hepatitis B virus surface antibody			
Negative	[redacted]	[redacted]	[redacted]

Positive	[redacted]	[redacted]	[redacted]
Hepatitis B virus core antibody			
Negative	[redacted]	[redacted]	[redacted]
Positive	[redacted]	[redacted]	[redacted]
Hepatitis C virus antibody			
Negative	[redacted]	[redacted]	[redacted]
Positive	[redacted]	[redacted]	[redacted]
Human immunodeficiency virus 1/2 antibody			
Non-reactive	[redacted]	[redacted]	[redacted]
Repeatedly reactive	[redacted]	[redacted]	[redacted]
Creatinine Clearance at Screening (mL/min)			
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; liso-cel: lisocabtagene maraleucel; SOC: standard of care.
Source: Abramson et al. (2023)[4]; Kamdar et al (2022);[112] BMS Data on File: TRANSFORM CSR (final DCO ; October 2023).[41]

Disease characteristics

The baseline disease characteristics for the ITT analysis set are summarised in Table 9 below. Baseline disease characteristics for the ITT analysis set were balanced between the liso-cel arm and the SOC arm.

Most patients (118 [64.1%]) had DLBCL histology at trial entry. Of these, 103 (56.0%) patients with DLBCL had de novo disease and 15 (8.2%) had transformed disease.[4] Transformed disease is disease that originated from a low-grade lymphoma and becomes a different type of lymphoma, most commonly DLBCL. Patients with other LBCL subtypes included 43 (23.4%) patients with HGBCL, 17 (9.2%) patients with PMBCL, five (2.7%) patients with THRBCL, and one (0.5%) patient with FL3B.[4]

The majority of patients (111 [60.3%]) had a sAAIPI score of 0 or 1 at screening, with the remaining 73 (39.7%) patients having a sAAIPI score of 2 or 3. In total, 137 (74.5%) of patients had primary refractory disease and 47 (25.5%) experiencing relapse ≤ 12 months after the initiation or completion of frontline therapy.[4] At baseline, the majority of patients (100 [54.3%]) had Stage IV disease according to the Ann Arbor staging system. [4]

Generally, UK clinical experts stated that the baseline disease characteristics of patients in the TRANSFORM trial were aligned with those of patients in UK clinical practice.[45]

Table 9: Key baseline disease characteristics

Number of treated patients, n (%)	SOC Arm (n=92)	Liso-cel Arm (n=92)	Total[a] (N=184)
Disease type at trial entry[b]			
DLBCL	58 (63.0)	60 (65.2)	118 (64.1)
FL3B	0	1 (1.1)	1 (0.5)
HGBCL	21 (22.8)	22 (23.9)	43 (23.4)
PMBCL	9 (9.8)	8 (8.7)	17 (9.2)

THRBCL	4 (4.3)	1 (1.1)	5 (2.7)
DLBCL subtype			
DLBCL NOS de novo	50 (54.3)	53 (57.6)	103 (56.0)
DLBCL from transformed indolent NHL	8 (8.7)	7 (7.6)	15 (8.2)
DLBCL subtype based on cell of origin			
GCB	40 (43.5)	45 (48.9)	85 (46.2)
ABC, Non-GCB	29 (31.5)	21 (22.8)	50 (27.2)
Unknown	23 (25.0)	25 (27.2)	48 (26.1)
NHL subtype based on chromosomal translocation			
Double hit lymphoma/triple hit lymphoma	[redacted]	[redacted]	[redacted]
Double hit lymphoma	[redacted]	[redacted]	[redacted]
Triple hit lymphoma	[redacted]	[redacted]	[redacted]
Non-double/triple hit lymphoma	[redacted]	[redacted]	[redacted]
Previous histology for DLBCL from transformed indolent NHL			
Transformed follicular lymphoma	[redacted]	[redacted]	[redacted]
Transformed marginal zone lymphoma	[redacted]	[redacted]	[redacted]
Immunohistochemistry expression status - n (%)[c]			
Sample utilised for local analysis			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
MYC translocation[d]			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Not Done	[redacted]	[redacted]	[redacted]
BCL2 translocation[d]			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
BCL6 translocation[d]			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Time from initial diagnosis to randomisation (months)			
Median	7.72	7.57	7.57
Time from start of last systemic regimen to randomisation (months)			
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Time from confirmation of CR during 1L treatment to relapse (months)[e]			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Min, max	[redacted]	[redacted]	[redacted]
Sum of product diameters (cm^2)			
n	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Sum of product diameters – n (%)			
> 50 cm^2	[redacted]	[redacted]	[redacted]
≤ 50 cm^2	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Lactate Dehydrogenase (LDH) - n (%)			
< 500 u/L	[redacted]	[redacted]	[redacted]
≥ 500 u/L	11 (12.0)	10 (10.9)	21 (11.4)
Missing	[redacted]	[redacted]	[redacted]
sAAIPI at screening - n (%)			
0 or 1	55 (59.8)	56 (60.9)	111 (60.3)
2 or 3	37 (40.2)	36 (39.1)	73 (39.7)
Prior response status - n (%)[f]			
Refractory	70 (76.1)	67 (72.8)	137 (74.5)
Relapse	22 (23.9)	25 (27.2)	47 (25.5)
Prior chemotherapy response status - n (%)[g]			
Chemorefractory	18 (19.6)	26 (28.3)	44 (23.9)
Chemosensitive	74 (80.4)	66 (71.7)	140 (76.1)
Bone marrow involvement (known or suspected) - n (%)			
Yes	13 (14.1)	9 (9.8)	22 (12.0)
No	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Confirmed CNS involvement - n (%)			
Yes	3 (3.3)	1 (1.1)	4 (2.2)
No	89 (96.7)	91 (98.9)	180 (97.8)
Ann Arbor stage - n (%)			
Stage I	14 (15.2)	8 (8.7)	22 (12.0)
Stage II	15 (16.3)	16 (17.4)	31 (16.8)
Stage III	13 (14.1)	18 (19.6)	31 (16.8)
Stage IV	50 (54.3)	50 (54.3)	100 (54.3)
Presence of B-symptoms - n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Number of extranodal involvement for DLBCL[h]			
n	[redacted]	[redacted]	[redacted]
Median	1.0	1.0	1.0

Min, max	[redacted]	[redacted]	[redacted]

[a] Contains all patients in the SOC arm or the liso-cel arm
[b] Based on WHO 2016 classification, as reported by Investigator (local laboratory) as specified on the eCRF
[c] Based on local laboratory
[d] Percentages are derived based on the samples utilised for analysis
[e] Number of lesions that are not in the lymph nodes
[f] Only patients with a best response of CR during 1L treatment are included
[g] The status is chemorefractory if a patient achieved SD or PD to last chemotherapy-containing regimen; otherwise, the status is chemosensitive
[h] The status is refractory if a patient achieved SD, PD, PR or CR with relapse before 3 months or relapsed if a patient achieved CR with relapse on or after lasting at least 3 months but no more than 12 months.
Abbreviations: 1L: first-line; ABC: activated B-cell; BCL2: B-cell lymphoma 2; BCL6; B-cell lymphoma 6; CR: complete response; CNS: central nervous system; CT: chemotherapy; DLBCL: diffuse large B-cell lymphoma; eCRF: electronic case report form; FL3B: follicular lymphoma grade 3B; GCB: geminal centre B-cell; HGBCL: high-grade B-cell lymphoma; LDH: lactate dehydrogenase; liso-cel: lisocabtagene maraleucel; MYC: myelocytomatosis oncogene; NHL: non-Hodgkins lymphoma; NOS: not otherwise specified; PMBCL: primary mediastinal large B-cell lymphoma; sAAIPI: secondary age-adjusted International Prognostic Index: SOC: standard of care; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma: WHO: world health organization.
Source: Abramson *et al.* (2023);[4] Kamdar *et al* (2022);[112] BMS Data on File: TRANSFORM CSR (final DCO ; October 2023).[41]

Concomitant medications

The concomitant medications used in TRANSFORM for the safety analysis set are summarised in Table 10 below. The medications used for the safety analysis set were generally balanced between the liso-cel arm and the SOC arm.

Table 10: Concomitant medication usage, SAS

Number of treated patients, n (%)	SOC Arm (n=91)	Liso-cel Arm (n=92)	Total[a] (N=183)
Patients with at least one concomitant medication	[redacted]	[redacted]	[redacted]
Alimentary tract and metabolism medication	[redacted]	[redacted]	[redacted]
Anti-infectives for systemic use	[redacted]	[redacted]	[redacted]
Antineoplastic and immunomodulating agents	[redacted]	[redacted]	[redacted]
Antiparasitic products, insecticides and repellents	[redacted]	[redacted]	[redacted]
Blood and blood forming organ medication	[redacted]	[redacted]	[redacted]
Cardiovascular system medication	[redacted]	[redacted]	[redacted]
Dermatologicals	[redacted]	[redacted]	[redacted]
Genito urinary system and sex hormones	[redacted]	[redacted]	[redacted]
Musculo-skeletal system medication	[redacted]	[redacted]	[redacted]
Nervous system medication	[redacted]	[redacted]	[redacted]
Respiratory system medication	[redacted]	[redacted]	[redacted]
Sensory organ medication	[redacted]	[redacted]	[redacted]
Systemic hormonal preparations, excluding sex hormones and insulins	[redacted]	[redacted]	[redacted]
Various	[redacted]	[redacted]	[redacted]

Abbreviations: SAS: safety analysis set; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Patient disposition

As of the final DCO (October 2023), the median follow-up was 33.9 months (range [redacted]. All 184 patients recruited into the trial underwent leukapheresis before being randomly assigned to the liso-cel or SOC arm, with 92 patients in each arm.

Liso-cel arm

Prior to liso-cel infusion, patients received optional bridging therapy and LDC. Fifty-eight (63.0%) patients in the liso-cel arm received bridging therapy.[4, 112] The most common reasons for receiving bridging therapy, as per investigator assessment, were high tumour burden (28 patients [48%]) and rapid progression (23 patients [40%]).[4] Of the 58 patients who received bridging therapy, [redacted] patients ([redacted]%) received R-DHAP, [redacted] patients ([redacted]%) received R-ICE and [redacted] patients ([redacted]%) received R-GDP.[41] The remaining 34 patients (37.0%) did not receive bridging therapy.[4, 41] In total, [redacted] patients ([redacted]%) discontinued before starting LDC with the remaining [redacted] patients ([redacted]%) completing all LDC treatments.[41]

In the liso-cel arm, 89/92 patients (96.7%) received liso-cel infusion (of the remaining three patients: one withdrew consent, one had a manufacturing failure and one received a non-conforming CAR-T product), with nine of those who received liso-cel experiencing relapse (n=6) or death (n=3) during the 18-week treatment period.[4, 41]

SOC arm

In the SOC arm, 91/92 patients (98.9%) were treated with re-induction therapy (one withdrew consent), 43/92 patients (46.7%) completed HDCT and ASCT and 61/92 patients (66.3%) were approved for crossover to receive liso-cel.[4, 41] The re-induction regimens received were R-DHAP ([redacted] patients [[redacted]%], R-ICE (58 patients [[redacted]%]) and R-GDP ([redacted] patients [[redacted]%]).[41] The primary reason for discontinuation of treatment in the SOC arm was lack of efficacy to re-induction therapy, which was experienced by 28 patients (30.4%), followed by disease relapse before receiving HDCT and ASCT, which was experienced by 15 patients (16.3%).[41]

Cross-over

Considering the 61 (66.3%) patients who crossed-over from the SOC arm to receive CAR-T cell therapy, reasons for cross-over included progression ([redacted] patients [[redacted]), relapse ([redacted] patients [[redacted]) and suboptimal response to SOC (8 patients [[redacted]).[41] Of the 61 patients approved for crossover, 58 were infused with liso-cel (including one patient who received a non-conforming product).[4] The median time from randomisation to approval of crossover was [redacted] and the median time from discontinuation of SOC to infusion of liso-cel was [redacted], which was shorter than in the liso-cel arm because the product manufacturing started before randomisation for all patients.[4] The [redacted] of patients in the crossover analysis set received liso-cel and completed the treatment period ([redacted]), with the remaining patients discontinuing during the 18-week period due to adverse event ([redacted]), death ([redacted]) or disease relapse ([redacted]).[41]

A detailed breakdown of patient disposition in TRANSFORM is reported in Appendix M.

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

B.2.4.1 Data sets

A total of 184 patients were included in the TRANSFORM trial cohort. A description of the study populations used for the analysis of outcomes from the TRANSFORM trial presented in this submission are provided in Table 11.

Table 11: Summary of data sets analysed

Study population	Description
ITT analysis set (n=184)	All patients randomised to a treatment arm. All efficacy analyses are performed on the ITT
Safety analysis set (n=183)	All patients who had taken at least one dose of study treatment. Reporting done on safety analysis set was done against actual treatment received **SOC SAS:** • Patients who received any treatment (e.g., re-induction immunochemotherapy with or without HDCT or ASCT) **Liso-cel SAS:** • Patients who received any study treatment, including bridging therapy if needed, lymphodepleting CT, and liso-cel or non-conforming product
HRQoL analysis set (n=[redacted])	All patients from the ITT population who completed a baseline and at least one post-baseline HRQoL assessment
Cross-over analysis set (n=61)	All patients of the ITT analysis set randomised to SOC who crossed over to liso-cel

Abbreviations: ASCT: autologous stem cell transplant; CT: chemotherapy; HDCT: high-dose chemotherapy; HRQoL: health-related quality of life; ITT: intention-to-treat; liso-cel: lisocabtagene maraleucel; SAS: statistical analysis system; SOC: standard of care.
Source: BMS Data on File: TRANSFORM Protocol[115]; Abramson *et al.* (2023).[4]

B.2.4.2 Statistical analyses

The statistical analyses used in TRANSFORM, alongside sample size calculations and methods for handling missing data, are presented in Table 12.

Table 12: Statistical methods for the primary analysis for TRANSFORM

Hypothesis objective	• The primary efficacy analysis was performed by testing the null hypothesis that there would be no difference in EFS between the treatment arm and control arm (i.e. HR=1)
Statistical analysis	• A hierarchical testing strategy (also called fixed-sequence method) was used to control the family-wise type I error rate for the primary and key secondary endpoints. The primary efficacy endpoint EFS was analysed first. If the null hypothesis for EFS could be rejected, then hypothesis testing on CRR and subsequently on PFS and OS would be performed hierarchically. No further testing was allowed once the testing sequence breaks (i.e. subsequent hypothesis cannot be rejected) • The O'Brien-Fleming boundary alpha spending function was used to adjust for multiplicity for the interim analysis for efficacy and the primary analysis. The null hypothesis was rejected if the p-value associated to the test is smaller than or equal to 0.024 at the time of the primary efficacy analysis. The alpha spending function used ensures that the overall type I error rate for the study is 2.5% **Primary endpoint** • EFS was analysed with a stratified Cox-PH model if the proportional hazards assumption holds (unstratified Cox-PH model as supportive analysis). The stratification factors to be used in the Cox-PH model were in line with the stratification at the time of randomisation (see Section B.2.3.1); in addition, the model included treatment as the only covariate for analysis • The proportional hazards assumption was evaluated via inspection of Schoenfeld residuals.[116] If non-proportional hazards are observed to the extent that a hazard ratio will not reliably represent the differences between treatment arms then a restricted mean survival approach or piecewise stratified Cox-PH model will be also investigated as sensitivity analysis • The null hypothesis was rejected if the p-value associated to the test was smaller than or equal to 0.024 at the time of the primary efficacy analysis (i.e., when 119 EFS events were observed) **Secondary endpoints** • If the null hypothesis of HR equal to 1 was rejected for EFS, hypothesis testing on CRR (and subsequently on PFS and OS) was performed hierarchically; the hierarchical testing strategy was used in order to control the overall type I error rate • The significance threshold to reject the null hypothesis for the key secondary endpoints was ≤0.021 at the primary analysis (per the O'Brien-Fleming boundary alpha spending function) • For time-to-event end points, the Kaplan-Meier product limit was used to provide summarised information and 95% CIs; time-to-event rates were computed using the Greenwood formula. HRs were estimated using a stratified Cox proportional hazards model

	• For OS, as patients from the SOC arm had the possibility to crossover to liso-cel, hence a 2-stage Weibull approach, also called 2-stage accelerated failure time model, and a rank-preserving structural failure time (RPSFT) model were investigated as supportive analyses in addition to those based on the ITT principle (i.e., ignoring cross over). These methodologies aim to estimate survival times that would have been observed in the SOC arm had the crossover not occurred. A stratified Cox proportional hazards regression model was fitted to the observed liso-cel arm survival times and the counterfactual SOC arm survival times to estimate a crossover-adjusted HR • For CRR, a Cochran-Mantel-Haenszel test with stratification factors as strata was used for analysis and calculation of p-values
Sample size, power calculation	**Sample size** • It was hypothesised that patients treated with SOC would have a median EFS of 3 months. Patients receiving liso-cel were expected to have an increase of ~81% in median EFS (equivalent to a HR of 0.55 under the exponential distribution assumption) compared to patients treated with SOC, bringing the median EFS in the experimental group to 5.455 months • Given these assumptions, using a log rank test with 2.5% one-sided significance level, 119 EFS events provided at least 90% power to reject the null hypothesis of HR greater than or equal to 1 • Given the expected randomisation rate of up to 12 patients per month, a 20% dropout rate before week 9 response assessment and a yearly dropout rate of 10% (30% cumulative), a sample size of 182 patients was randomised and 215 patients were screened (assuming a screen failure rate of 15%) **Power calculation** • Considered independently, performed at the same time of the primary efficacy analysis and with the same randomisation and dropout model, expected power would be over 98% for CRR assuming a rate of 22% in the SOC arm and 51% in the liso-cel arm, over 96% for PFS assuming a median of 3 months in the SOC arm and 6 months in the liso-cel arm (HR=0.5), and approximatively 36% for OS assuming a rate at 2 years of 41% in the SOC arm and 56% in the liso-cel arm (HR=0.65) • Factoring in the hierarchical structure in the power calculation, and assuming the same rates for CRR, the same median survivals for PFS and the same rates at 2 years for OS mentioned above, the expected power would be 90% for testing EFS, 88% (0.90*0.98) for testing CRR, 85% (0.90*0.98*0.96) for testing PFS and 31% (0.90*0.98*0.96*0.37) for testing OS
Data management, patient withdrawals	**Discontinuation and withdrawal:** • The reason for discontinuation of treatment was recorded in the case report form (CRF) and in the source documents • Patients who withdrew from the trial or discontinued treatment were censored as per the approaches outlined below **Data censoring was applied for the primary endpoint and key secondary endpoints (CRR, PFS and OS) as follows:** • For the EFS calculation, data was censored: o At the randomisation date if there was no baseline, or no post-baseline response assessment and no death

	○ At the last disease evaluation if the patient started a new antineoplastic therapy for reasons other than efficacy concerns ○ At the last disease evaluation if the patient failed to proceed to HDCT and ASCT due to refusal or failure to collect or mobilise stem cells ○ At the last disease evaluation if there was no death, no progressive disease, no failure to achieve CR or PR by 9 weeks post-randomisation (after 3 cycles of SOC or 5 weeks after liso-cel infusion) • For the PFS calculation, data was censored: ○ At the randomisation date if there was no baseline, or no post-baseline response assessment and no death ○ At the last disease evaluation if the patient started a new antineoplastic therapy for reasons other than efficacy concerns ○ At the last disease evaluation if there was no death or progressive disease • For the OS calculation, data was censored: ○ At the last date the patient was known to be alive for any patients alive or lost to follow up at the time of analysis • For the CRR calculation, patients with unknown or missing response were counted as non-evaluable in the analysis. Any responses after a start of a new antineoplastic therapy taken for efficacy concerns were not considered. All new antineoplastic therapies were considered as being started for efficacy concerns, unless explicitly recorded as not been given for efficacy concerns on the appropriate CRF

Abbreviations: ASCT: autologous stem cell transplant; CI: confidence interval; Cox PH: Cox proportional hazards; CRF: case report form; CR: complete response; CRR: complete response rate; EFS: event-free survival; HDCT: high-dose chemotherapy; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PFS: progression-free survival; PR: partial response; RPSFT: rank-preserving structural failure time; SOC: standard of care.
Source: BMS Data on File: TRANSFORM Protocol.[115]

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

A summary of the quality of the TRANSFORM trial, using the NICE checklist is presented in Table 13.[117] The overall risk of bias in the TRANSFORM trial was considered to be low.

The results of the quality assessments for all other RCTs identified in the clinical SLR are presented in Appendix D.

Table 13: Quality assessment of the TRANSFORM trial

Question	Risk of bias	Justification
Was randomisation carried out appropriately?	Low	Randomisation was done with a permuted-blocks method with interactive response technology (IRT) managed by an external vendor and stratified by response to first-line therapy and secondary age-adjusted International Prognostic Index
Was the concealment of treatment allocation adequate?	High	TRANSFORM was an open-label study and therefore treatment allocations were not concealed
Were the groups similar at the outset of the study in terms of prognostic factors?	Low	Baseline characteristics were well-balanced between treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	High	TRANSFORM was an open-label study and therefore treatment allocations were not concealed
Were there any unexpected imbalances in drop-outs between groups?	Low	Of the 184 patients randomised, 180 received treatment. Of the 4 patients who did not receive treatment, three were in the liso-cel arm and one was in the SOC arm
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	All pre-specified outcomes were measured and reported. There is no evidence which suggests that more outcomes were measured.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low	All outcomes reported in the methods were described in the results

Source: York CRD (2009).[117]

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

B.2.6.1 Data cuts

Four interim analyses (IAs) of TRANSFORM trial data were planned:

- IA1 was conducted when ~30 evaluable patients (~15 patients per arm and having received their assigned treatment) had their 9 Week response assessment (after 3 cycles of SOC for the SOC arm or 5 weeks after the liso-cel infusion) or had been confirmed with disease progression prior to this timepoint. The purpose of this analysis was to allow the trial to stop for futility
- IA2 was planned at approximately 60% information fraction for EFS and was actually performed at 63% information fraction (75 EFS events; DCO November 2020). The purpose of this analysis was to demonstrate superiority of liso-cel versus SOC on EFS
- IA3 was conducted at approximately 80% information fraction and was added as an additional interim analysis following review for IA2. Results of the 80% analysis, which was actually performed at 82% information fraction (98 EFS events; DCO March 2021), are reported in Kamdar *et al*. (2022)[112]
- IA4 was the primary analysis for EFS and was performed at 119 EFS events; results of the primary analysis (DCO May 2022) are reported in Abramson *et al.* (2023)[4]
- A final efficacy analysis was performed when the last patient randomised has reached an event or the end of the trial (final DCO; October 2023)
    - No p-value is available for OS from the final DCO (October 2023) as hypothesis testing for OS was not conducted for this DCO. The decision not to re-test OS in this analysis was because too much of the alpha was considered to have been "spent" in the interim and primary analyses such that conducting formal tests in this analysis could risk inflating the overall Type I error rate, potentially leading to invalid conclusions

The results from the final efficacy analysis (DCO October 2023), are presented in this section and are available in the abbreviated CSR provided in the reference pack.

B.2.6.2 Primary endpoint

EFS based on IRC assessment

Liso-cel showed a statistically significant reduction in the relative risk of the primary endpoint, EFS, by 62% compared with SOC

EFS was defined as the time from randomisation to progressive disease, failure to achieve CR or PR by 9 weeks post-randomisation, start of a new antineoplastic therapy due to efficacy concerns or death from any cause, whichever occurs first. The primary endpoint of EFS is an established endpoint which classes a best 'response' of SD and new therapy commencement prior to radiographic disease progression as an event, alongside disease progression and death. This is the most clinically relevant endpoint in a curable disease setting where SD is not an acceptable outcome and where patients with suboptimal response to treatment will be moved onto a new therapy for potential cure at the earliest opportunity.[5] UK clinical experts agreed EFS was the most relevant endpoint in this indication for the reasons outlined above.[45]

At the time of IA3 (March 2021 DCO), with median follow-up 6.2 months and 82% information fraction (see Section B.2.6.1), liso-cel met the primary endpoint for EFS. Median EFS was significantly improved in the liso-cel arm (10.1 months [95% CI: 6.1, NR]) compared with the

SOC arm (2.3 months [95% CI: 2.2, 4.3]); stratified HR: 0.35; 95% CI: 0.23, 0.53; one-sided p<0.0001).[112] KM curves from the primary analysis (March 2021 DCO) can be found in Appendix M.1.3.

With longer follow-up, at the time of the final efficacy analysis (DCO October 2023) with median follow up 33.9 months, [redacted] EFS events by independent review occurred for [redacted] in the liso-cel arm and [redacted] in the SOC arm. Liso-cel was superior to SOC, with a stratified HR of 0.38 (95% CI: 0.26, 0.54; see Table 14).[41]

The median EFS was longer in the liso-cel arm (29.5 months; 95% CI: 9.5, NE) than in the SOC arm (2.4 months; 95% CI: 2.2, 4.9). The estimated EFS at 36 months was 45.8% (95% CI: 35.2, 56.5) in the liso-cel arm compared with 19.1% (95% CI: 11.0, 27.3) in the SOC arm.[41]

As shown in the Kaplan-Meier plot (Figure 6), there is a clear separation between EFS curves in the liso-cel and SOC arms by approximately [redacted] from randomisation. There is evidence that the liso-cel EFS curve plateaus at around [redacted] from randomisation once approximately [redacted] of patients had reached an event, whereas the SOC EFS curve plateaus when approximately [redacted] of patients had reached an event at around [redacted] from randomisation.[41]

The most common EFS events in either the liso-cel or SOC arms were disease progression ([redacted], respectively), failure to achieve CR or PR by 9 weeks post-randomisation ([redacted], respectively), start of a new anti-cancer therapy due to efficacy concerns [redacted], respectively), and death from any cause ([redacted] respectively).[41]

Findings of the EFS sensitivity analyses were supportive of and consistent with results for the primary analysis of EFS (see Section B.2.7). Details on the primary analysis from the previous DCO (March 2021) can be found in Appendix M.1.3.

Figure 6: Kaplan-Meier plot for EFS based on IRC assessment, ITT

Footnotes: Arm A = SOC arm; Arm B = liso-cel arm.
Abbreviations: CI: confidence interval; EFS: event free survival; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 14: Summary of EFS results based on IRC assessment, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Patients with events, n (%)	[redacted]	[redacted]
Median time to event (months; 95% CI)[a]	2.4 (2.2, 4.9)	29.5 (9.5, NE)
Stratified HR (95% CI)[b]	0.375 (0.259–0.542)	
12-month EFS rate, % (SE)	[redacted]	[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
24-month EFS rate, % (SE)	[redacted]	[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
36-months EFS rate, % (SE)	19.1[redacted]	45.8[redacted]
Two-sided 95% CI[c]	11.0, 27.3	35.2, 56.5

Footnotes: [a] Median estimates of time to event are from Kaplan-Meier product limit estimates. [b] Based on stratified Cox proportional hazards model. [c] Greenwood's formula.
Abbreviations: CI: confidence interval; EFS: event-free survival; HR: hazard ratio; IRC: independent review committee; liso-cel: lisocabtagene maraleucel; SE: standard error; SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.6.3 Secondary endpoints

Complete and objective response rates based on IRC assessment

CRR was defined as the proportion of patients achieving a best overall response of CR and ORR was defined as the proportion of patients achieving a best overall response of PR or CR. CRR is therefore the most clinically relevant endpoint in a curable disease setting as CR is the term used for the absence of all detectable cancer following treatment.

At the time of the primary analysis (DCO May 2022), with a median follow up of 17.5 months, liso-cel met the key secondary endpoint of CRR. The liso-cel arm demonstrated a statistically significant improvement in CRR compared to the SOC arm: CRR in the liso-cel and SOC arms were 73.9% (95% CI: 63.7, 82.5) and 43.5% (95% CI: 33.2, 54.2) respectively; the stratified one-sided p-value was <0.0001.[4]

CRR and ORR did not change between the May 2022 DCO and the final DCO (October 2023). At the time of the final DCO (October 2023), the CRR for the liso-cel arm remained 30.4% higher in the liso-cel arm versus the SOC arm (73.9% [n=68/92] and 43.5% [n=40/92], respectively); see Table 15. The ORR for the liso-cel arm was 38.1% higher than the SOC arm (87.0% [n=80/92] and 48.9% [n=45/92], respectively).[41]

Table 15: Summary of best overall response, ORR and CRR based on IRC assessment, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Best overall response, n (%)		
CR	40 (43.5)	68 (73.9)
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Non-evaluable	[redacted]	[redacted]
CRR, n (%)	40 (43.5)	68 (73.9)
Two-sided 95% CI	33.2, 54.2	63.7, 82.5
ORR, n (%)	45 (48.9)	80 (87.0)
Two-sided 95% CI	38.3, 59.6	78.3, 93.1

Abbreviations: CI: confidence interval; CR: complete response; CRR: complete response rate; IRC: independent review committee; ITT: intention-to-treat; liso-cel: lisocabtagene maraleucel; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease.
Sources: Abramson *et al.* (2023);[4] BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Duration of response based on IRC assessment

DOR was defined as the time from first relapse to disease progression, start of antineoplastic therapy due to efficacy concerns or death, whichever occurs first. This represents the length of time that a tumour continues to respond to treatment without the cancer growing or spreading, indicating the ability of a treatment to control the disease.

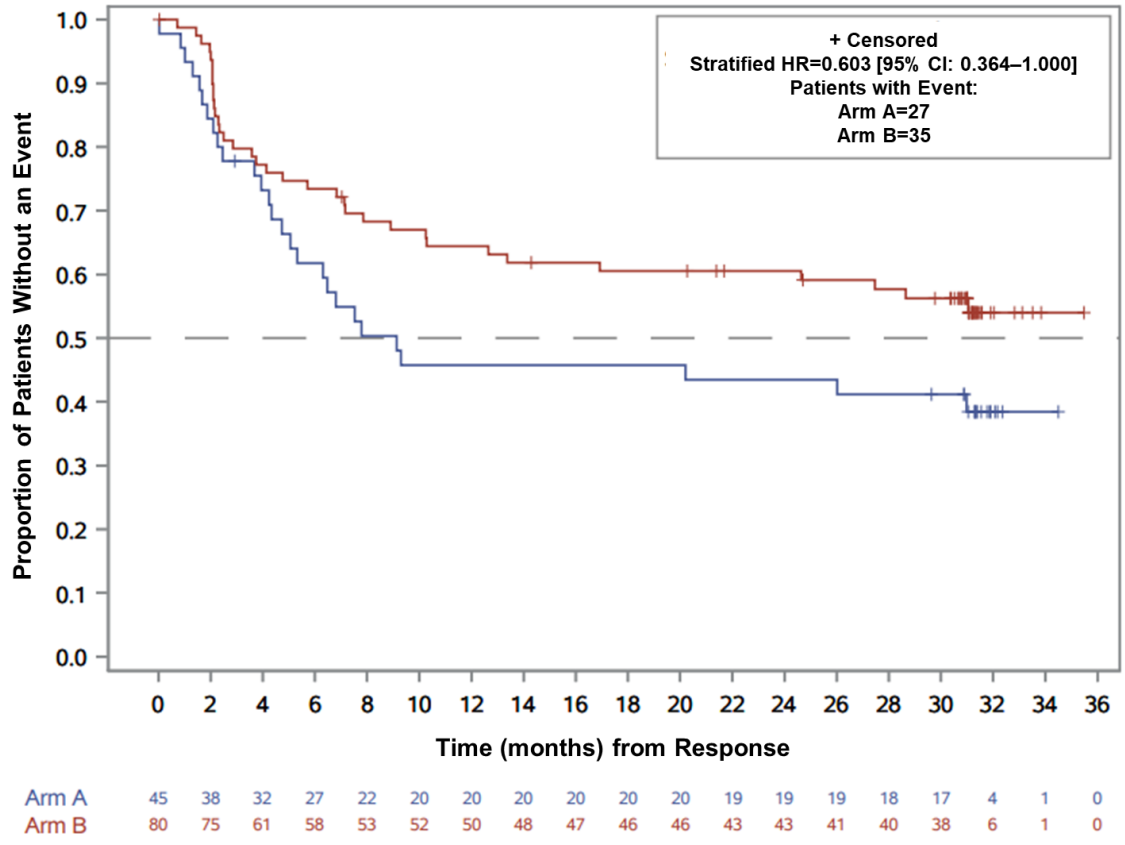
At the time of the primary analysis (DCO May 2022), with a median follow up of 17.5 months, DOR events occurred for 31/80 (39%) patients in the liso-cel arm and 25/45 (56%) patients in the SOC arm. DOR was longer for the liso-cel arm compared to the SOC arm (stratified HR: 0.58 [95% CI: 0.34, 0.98]).[4] The median duration of CR (DoCR) was 9.1 months (95% CI: 5.1, not

reached) in the SOC arm and was not reached (95% CI: 13.4, not reached) in the liso-cel arm (HR: 0.48 [95% CI: 0.26, 0.89]).[4]

At the time of the final DCO (October 2023), with a median follow-up of 33.9 months, DOR events occurred for 35 (38.0%) patients in the liso-cel arm and 27 (29.3%) patients in the SOC arm; see Table 16. DOR was longer for the liso-cel arm compared to the SOC arm (stratified HR: 0.60 [95% CI: 0.36, 1.00]). The estimated DOR at 24 months was 60.5% (95% CI: 49.7, 71.4) in the liso-cel arm compared to 43.5 (95% CI: 28.8, 58.1) in the SOC arm; Figure 9.[41]

The median DoCR was 9.30 months (95% CI: 5.06, not reached) in the SOC arm and was not reached (95% CI: 28.65, not reached) in the liso-cel arm (HR: 0.50 [95% CI: 0.28, 0.89]), demonstrating more sustained disease control with liso-cel.[41]

Figure 7: Kaplan-Meier plot of DOR based on IRC assessment, ITT



Footnotes: Arm A = SOC arm; Arm B = liso-cel arm.
Abbreviations: CI: confidence interval; DOR: duration of response; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 16: Summary of DOR based on IRC assessment, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Patients with events, n (%)	27 (29.3)	35 (38.0)
Median time to event (months; 95% CI)[a]	9.1 (5.1, NE)	NE (16.9, NE)
Stratified HR (95% CI)[b]	0.603 (0.364, 1.000)	
12-month DOR rate, % (SE)	45.8 [redacted]	64.4 [redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
24-month DOR rate, % (SE)	43.5[redacted]	60.5[redacted]
Two-sided 95% CI[c]	28.8, 58.1	49.7, 71.4

Footnotes: [a] Median estimates of time to event are from Kaplan-Meier product limit estimates. [b] Based on stratified Cox proportional hazards model. [c] Greenwood's formula.
Abbreviations: CI: confidence interval; DOR: duration of response; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat; liso-cel: lisocabtagene maraleucel; NE: not evaluable; SE: standard error: SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

PFS based on IRC assessment

PFS was defined as the time from randomisation to death from any cause or progressive disease, whichever occurs first. Although useful, PFS is a less clinically relevant endpoint than EFS given the curative intent of treatment. In this indication, SD is not considered a successful treatment outcome, and therefore, patients who remain progression-free but with SD are moved onto receive a subsequent treatment line. In TRANSFORM, these patients could crossover into the liso-cel arm, with a median time from progression to liso-cel infusion of [redacted], and as a result, any comparison of PFS between liso-cel and SOC is likely to be biased. PFS results are biased by informative censoring as patients who received a new treatment were censored from the PFS analysis if this occurred before progression in TRANSFORM.[118] As initiation of a new treatment is not random and is related to a patient's prognosis, this results in an overestimation of PFS, as the outcome is reflective of patients with a better prognosis.

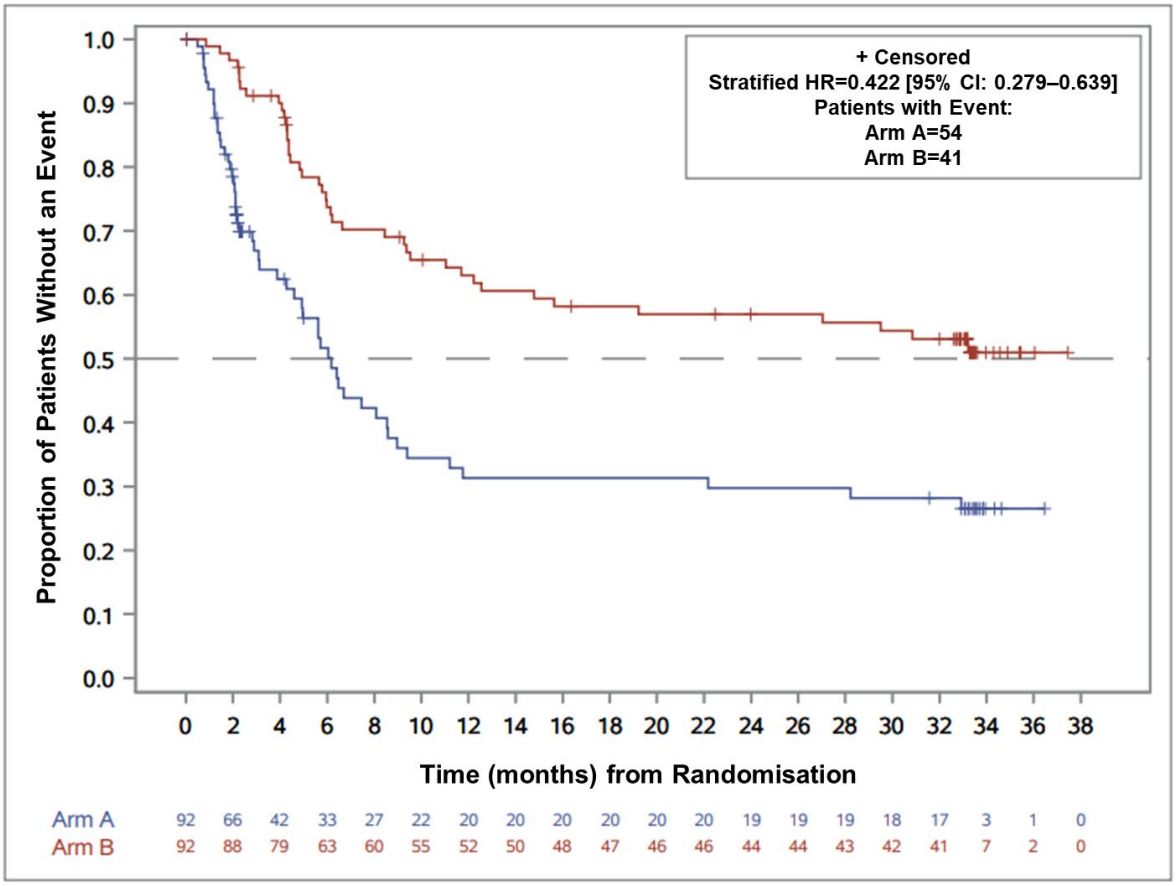
In the primary analysis DCO (May 2022), with a median follow-up of 17.5 months, liso-cel met the key secondary endpoint of PFS. The liso-cel arm demonstrated a statistically significant improvement in PFS compared to the SOC arm: HR=0.40 (95% CI: 0.26, 0.62); p-value (based on a stratified Cox-PH model)<0.0001.[4]

With longer follow-up, at the time of the final DCO (October 2023), with a median follow-up of 33.9 months, 41 patients (44.6%) in the liso-cel arm and 54 patients (58.7%) in the SOC arm experienced disease progression or death. Liso-cel was superior to SOC, with a stratified HR of 0.422 (95% CI: 0.28, 0.64); see Table 17. The estimated PFS at 36 months was 50.9% (95% CI: 39.9, 62.0) in the liso-cel arm compared with 26.5% (95% CI: 15.9, 37.1) in the SOC arm.[41]

As shown in the Kaplan-Meier plot (Figure 8), there is a clear separation between PFS curves in the liso-cel and SOC arms by approximately Month 3 from randomisation. There is evidence that the liso-cel PFS curve plateaus at around Month 13, once approximately 40% of patients had experience disease progression or death, whereas the SOC PFS curve plateaus when approximately 65% of patients had experienced disease progression or death at around Month 9 from randomisation.[41]

Disease progression in the liso-cel and SOC arms occurred in [redacted] of patients, respectively and death from any cause occurred in [redacted] of patients, respectively.[41]

Figure 8: Kaplan-Meier plot for PFS based on IRC assessment, ITT



Footnotes: Arm A = SOC arm; Arm B = liso-cel arm.
Abbreviations: CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat; PFS: progression-free survival.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 17: Summary of PFS results based on IRC assessment, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Patients with events, n (%)	54 (58.7)	41 (44.6)
Median time to event (months; 95% CI)[a]	6.2 (4.3, 8.6)	NE (12.6, NE)
Stratified HR (95% CI)[b]	0.422 (0.279, 0.639)	
12-month PFS rate, % (SE)	31.3[redacted]	63.0[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
24-month PFS rate, % (SE)	29.7[redacted]	57.0[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
36-month PFS rate, % (SE)	26.5[redacted]	50.9[redacted]
Two-sided 95% CI[c]	15.9, 37.1	39.9, 62.0

Footnotes: [a] Median estimates of time to event are from Kaplan-Meier product limit estimates. [b] Based on stratified Cox proportional hazards model. [c] Greenwood's formula.
Abbreviations: CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-

treat; liso-cel: lisocabtagene maraleucel; NE: not evaluable; PFS: progression-free survival; SE: standard error; SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

PFS on the subsequent line of therapy (PFS-2) based on investigator's assessment

Progression-free survival on the subsequent line of therapy (PFS2) represents the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death from any cause.

At the time of the primary analysis (DCO May 2022), with a median follow-up of 17.5 months, 43 patients (46.7%) in the liso-cel arm and 63 patients (68.5%) in the SOC arm had a PFS2 event.[114] The majority of PFS2 events in both the liso-cel and SOC arms were first progression (41.3% and 65.2%, respectively) as in this indication, patients can receive a subsequent line of treatment without previously progressing on the previous line of therapy.[114] Similarly, for this reason, it is plausible that the number of PFS2 events is higher than the number of PFS events reported in Section B.2.6.3. The observed results indicated that liso-cel was superior to SOC, with a stratified HR of 0.56 (95% CI: 0.39, 0.81), although statistical significance was not formally tested. In addition, this result was confounded by high proportion (66.3%) of SOC patients who were approved for crossover to receive liso-cel as a subsequent treatment in TRANSFORM.[114]

At the time of the final DCO (October 2023), with a median follow-up of 33.9 months, [redacted] patients ([redacted]%) in the liso-cel arm and [redacted] patients ([redacted]%) in the SOC arm had a PFS2 event.[41] The majority of PFS2 events in both the liso-cel and SOC arms were first progression ([redacted]% and [redacted]%, respectively). While PFS2 was not formally tested for statistical significance, the observed results indicated that liso-cel was superior to SOC, with a stratified HR of [redacted] (95% CI: [redacted]). Further details on crossover adjustment are considered for OS in the following section.

These results demonstrate that the PFS benefit of liso-cel is maintained beyond the next line of therapy received and suggests the receipt of CAR-T therapy at 2L is associated with an improvement in outcomes compared to CAR-T therapy receipt at 3L+. A summary of PFS2 at a median follow-up of 33.9 months is presented in Table 18.[41]

Table 18: Summary of PFS-2 results based on investigator's assessment, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Patients with events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
First Progression	[redacted]	[redacted]
Second Progression	[redacted]	[redacted]
Number of events		
None	[redacted]	[redacted]
One	[redacted]	[redacted]
Two	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Randomisation	[redacted]	[redacted]
Last disease assessment	[redacted]	[redacted]
Stratified HR (95% CI)[a]	[redacted]	

Footnotes: [a] The Stratified HR is based on the intervals defined by the current line of therapy and the next line of therapy. Confidence intervals are derived using sandwich estimator.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

OS

OS was defined as the time from randomisation to death from any cause.

At the time of the primary analysis (DCO May 2022), 28 deaths in the liso-cel arm (30.4%) and 38 deaths in the SOC arm (41.3%) were reported.[4] The median OS was not reached in the liso-cel arm (95% CI: 29.5, not reached) and was 29.9 months in the SOC arm (95% CI: 17.9, not reached) resulting in a stratified OS HR of 0.72 (95% CI: 0.44, 1.18; p=0.099).[4] The estimated OS at 12 months and 18 months in the liso-cel arm was 83.4% and 73.1%, respectively, compared to 72.0% and 60.6%, respectively, in the SOC arm.[4]

At the time of the final DCO (October 2023), 34 deaths in the liso-cel arm (37.0%) and 42 deaths in the SOC arm (45.7%) were reported.[41] The median OS was NE in the liso-cel arm (95% CI: 42.8, NE) and the SOC arm (95% CI: 18.2, NE); see Table 19.[41] The estimated OS at two-years and three-years was 67.5% and 62.8%, respectively in the liso-cel arm compared to 58.2% and 51.8%, respectively in the SOC arm.[41]

As shown in the Kaplan-Meier plot (Figure 9), there is evidence that the liso-cel OS curve plateaus from around Month 30 onwards, when approximately 65% of patients were still alive, whereas the SOC OS curve plateaus when approximately 55% of patients were alive at around Month 34 from randomisation.[41]

The stratified OS HR of 0.76 (95% CI: 0.48, 1.19) indicates that liso-cel reduces the risk of death by 24% when compared to SOC.[41] This difference was not statistically significant but is confounded by the high proportion (66.3%) of SOC patients who crossed over to receive liso-cel as a subsequent treatment in TRANSFORM, potentially underestimating the OS improvement of 2L liso-cel compared to SOC.[4, 41]

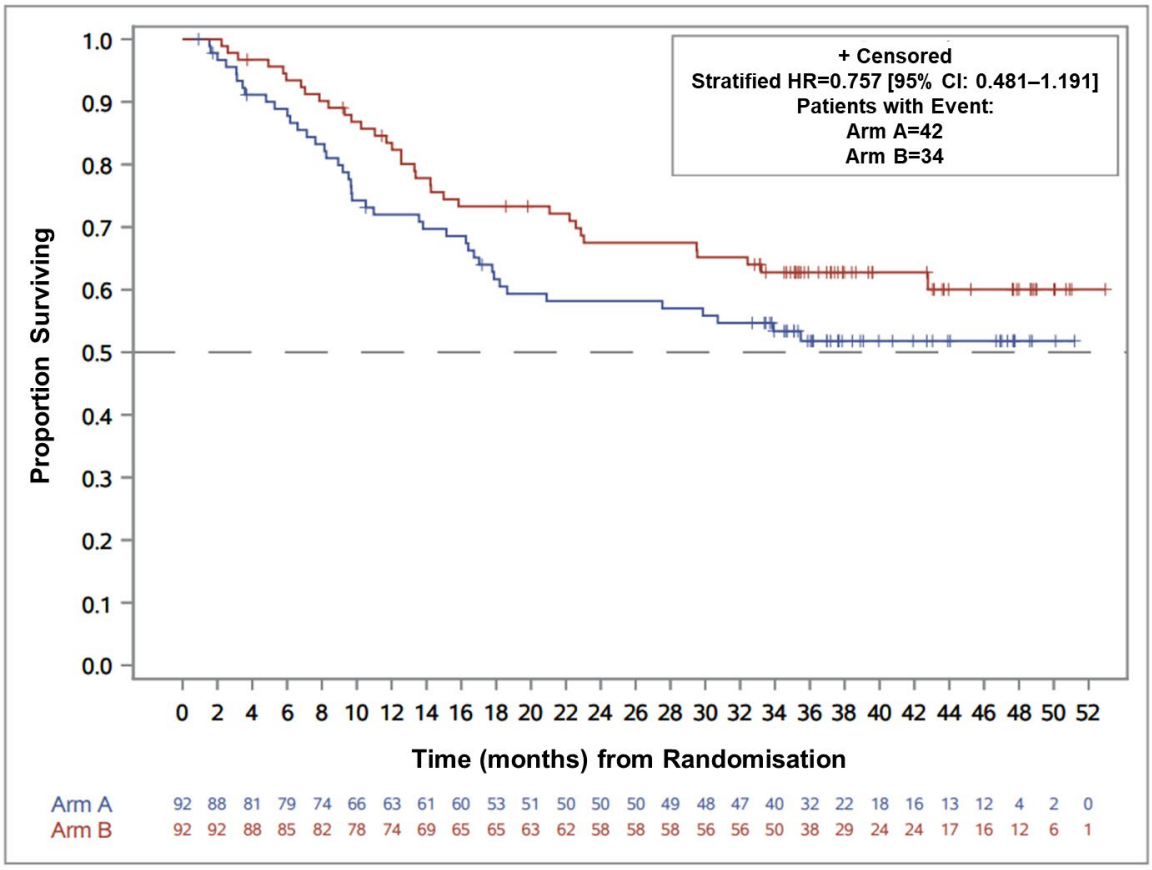
At the time of the primary analysis (DCO May 2022), crossover-adjusted analyses using the 2-stage accelerated failure time model and RPSFT subsequent-treatment adjustment methods, outlined in NICE TSD16, resulted in stratified OS HRs of 0.42 (95% CI: 0.25, 0.69) and 0.28 (95% CI: 0.15, 0.54), respectively.[4] At the final DCO (October 2023), the two analyses resulted in stratified OS HRs of 0.57 (95% CI: 0.36, 0.90) and [redacted] (95% CI: [redacted], [redacted]), respectively (see Table 20).[4, 119]

The subsequent therapies received in the SOC arm of TRANSFORM are aligned with UK clinical practice, as CAR-T therapy is the routine subsequent treatment after SOC in the UK, however it is worth noting that in the TRANSFORM trial patients received 3L+ CAR-T a median of [redacted] following progression, which would be much quicker than what would be expected in UK clinical practice.[41] This results in SOC outcomes being overestimated compared to clinical practice.

OS for patients receiving liso-cel is likely to be further underestimated relative to UK clinical practice; UK clinical experts confirmed the majority of patients who are not cured (64.5%) would receive novel 3L+ treatments, such as glofitamab (TA927) and epcoritamab (TA954),[45, 103, 120] following treatment with liso-cel which would be expected to improve outcomes for patients

receiving CAR-T at 2L. In the liso-cel arm of TRANSFORM, [redacted] This is discussed in greater detail in Section B.2.12.

Figure 9: Kaplan-Meier plot for OS, ITT



Footnotes: Arm A = SOC arm; Arm B = liso-cel arm.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 19: Summary of OS results, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
Patients with events, n (%)	42 (65.7)	34 (37.0)
Median time to event (months; 95% CI)[a]	NE (18.2, NE)	NE (42.8, NE)
Stratified HR (95% CI)[b]	0.757 (0.481, 1.191)	
12-month OS rate, % (SE)	72.0[redacted]	83.5[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
24-month OS rate, % (SE)	58.2[redacted]	67.5[redacted]
Two-sided 95% CI[c]	[redacted]	[redacted]
36-month OS rate, % (SE)	51.8[redacted]	62.8[redacted]
Two-sided 95% CI[c]	41.2, 62.4	52.7, 72.9

Footnotes: [a] Median estimates of time to event are from Kaplan-Meier product limit estimates. [b] Based on stratified Cox proportional hazards model. [c] Greenwood's formula.
Abbreviations: CI: confidence interval; HR: hazard ratio; NE: not evaluable; ITT: intention-to-treat; OS: overall survival; SE: standard error; SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 20: Stratified HR OS results for 2-stage accelerated failure time model and RPSFT, ITT

	SOC arm (n=92)	Liso-cel arm (n=92)
2-stage accelerated failure time model		
Stratified HR (95% CI)[a]	0.566 (0.359, 0.895)	
RPSFT		
Stratified HR (95% CI)[a]	[redacted]	

Footnotes: [a] Based on stratified Cox proportional hazards model.
Abbreviations: CI: confidence interval; HR: hazard ratio; NE: not evaluable; OS: overall survival; RPSFT: rank-preserving structural failure time; SOC: standard of care.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.6.4 Patient reported outcomes

Three HRQoL questionnaires were used to capture patient reported outcomes (PROs) at baseline and at scheduled assessments in TRANSFORM: the EORTC QLQ-C30, Functional Assessment of Cancer Therapy – Lymphoma subscale (FACT-Lym) and the EuroQoL 5-Dimensions (EQ-5D) questionnaire. Published HRQoL data from the March 2021 DCO for EORTC QLQ-C39 and FACT-Lym are in Appendix M, with data from the final DCO (October 2023) presented below.

The EORTC QLQ-C30 is an internationally validated and widely used measure designed to assess the HRQoL of cancer patients participating in clinical trials.[121] The 30-item measure considers the global health status, and the physical, role, emotional, cognitive, and social functioning of patients, as well as common cancer symptoms experienced by patients. A higher overall QLQ-C30 summary score indicates better HRQoL (range: 0 – 100).[121]

The FACT-Lym is a widely used lymphoma-specific questionnaire that captures QoL concerns relevant specifically to lymphoma patients (range: 0–60). This includes common disease and/or treatment-related symptoms such as pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite. A difference of ≥3 points can be considered to be a clinically meaningful minimally important difference (i.e. the smallest amount of change considered important to patients).[122]

The EQ-5D is a standardised measure of health status; specifically, the EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and each dimension has five response levels of severity. The EQ-5D-5L includes a visual analogue scale (VAS) which elicits an individual's rating of their own overall current health using a scale from 1 (the worst health you can imagine) to 100 (the best health you can imagine).[123]

EORTC QLQ-C30

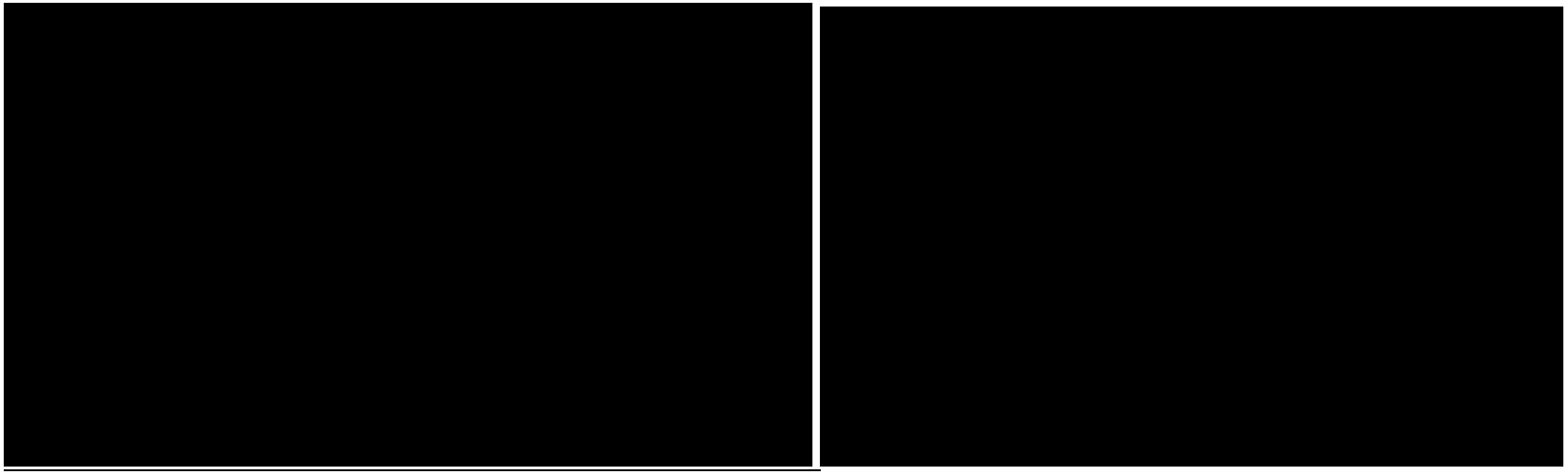
Changes in HRQoL from baseline for liso-cel versus SOC for global health domain

A summary of the change from baseline in EORTC QLQ-C30 global health domain scores and the mean change from baseline for patients in the liso-cel and SOC arms at different timepoints are presented in Figure 10.

In general, the EORTC QLQ-C30 global health domain scores for patients treated with liso-cel were [redacted] that of patients treated with SOC based on the final DCO (October 2023). Scores [redacted] in both treatment arms as the study progressed and at the end of the study, the global health domain scores were [redacted] for SOC compared with liso-cel. However, it should be noted there were [redacted] patients assessed at this timepoint in the SOC arm ([redacted]), and HRQoL data was no longer collected for patients who experienced an event and crossed over in TRANSFORM, meaning that HRQoL assessments for the SOC arm at the end of the study likely reflect those patients who have experienced the best responses to SOC, and may not reflect the experiences of the SOC arm as a whole. Generally, these PRO results demonstrate that liso-cel, compared to SOC, [redacted] patient HRQoL throughout the course of treatment.

Similar trends were also observed for the fatigue, pain, physical functioning and cognitive functioning domains of EORTC QLQ-C30, which are presented below.

Figure 10: Shift from baseline in EORTC QLQ-C30 global health domain scores by treatment and timepoint (October 2023 DCO)

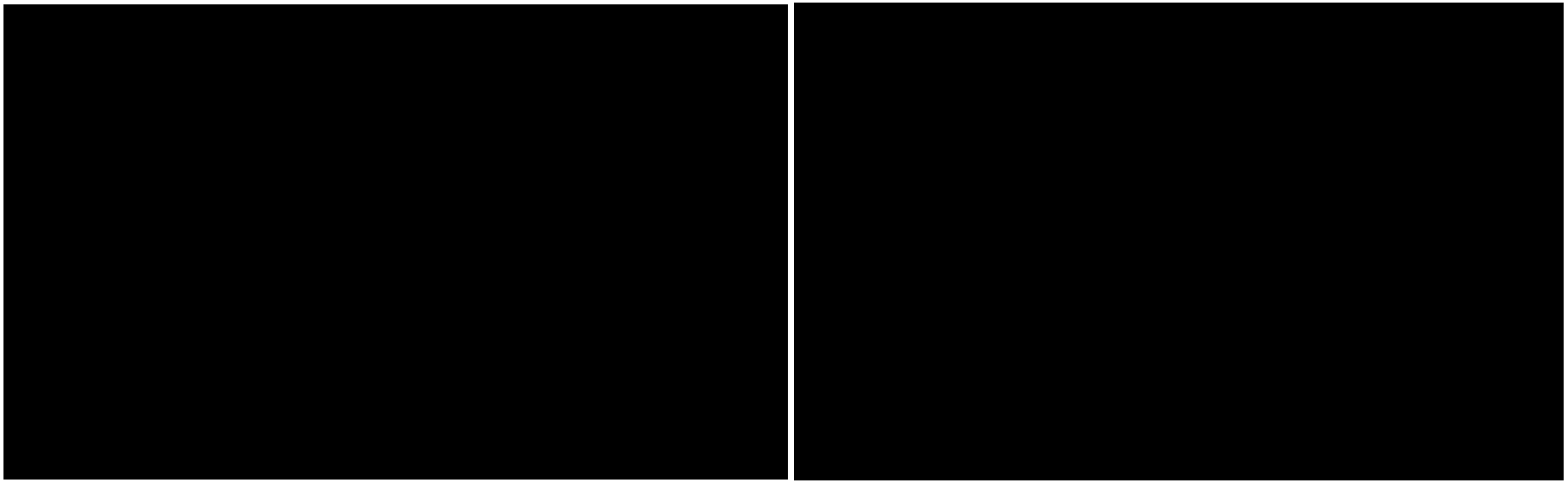


Footnotes: Arm A = SOC and Arm B = liso-cel.
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Changes in HRQoL from baseline for liso-cel versus SOC for fatigue domain

A summary of the change from baseline in EORTC QLQ-C30 fatigue scores and the mean change from baseline for patients in the liso-cel and SOC arms at different timepoints are presented in Figure 11.

Figure 11: Shift from baseline in EORTC QLQ-C30 fatigue scores by treatment and timepoint (October 2023 DCO)

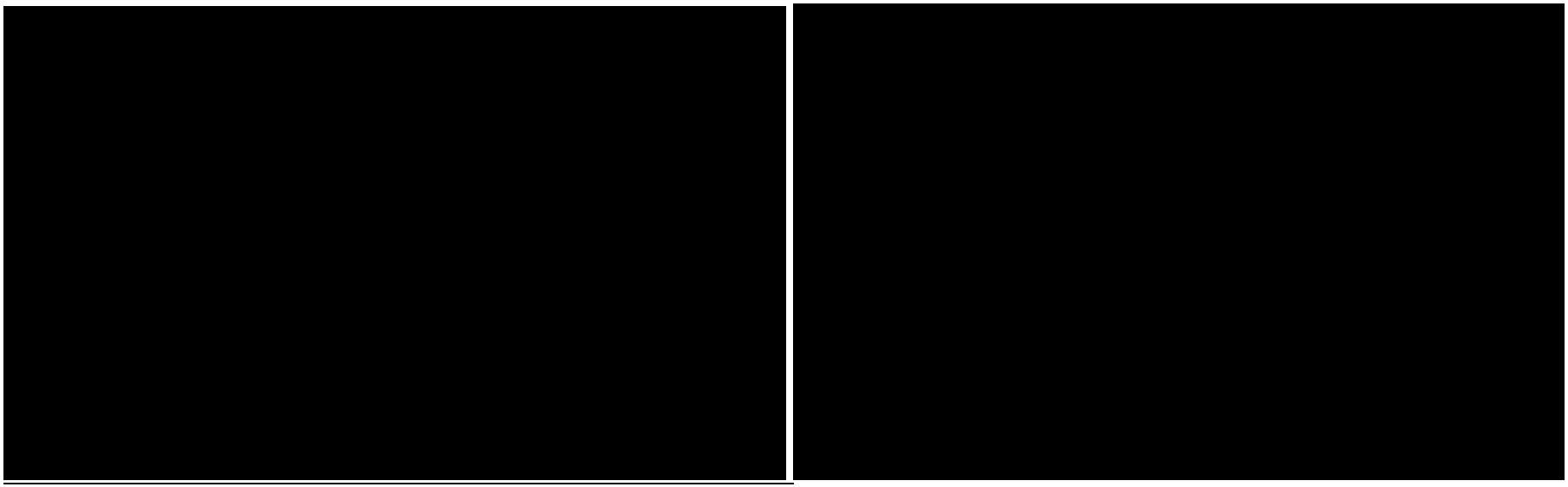


Footnotes: Arm A = SOC and Arm B = liso-cel.
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Changes in HRQoL from baseline for liso-cel versus SOC for pain domain

A summary of the change from baseline in EORTC QLQ-C30 pain scores and the mean change from baseline for patients in the liso-cel and SOC arms at different timepoints are presented in Figure 12.

Figure 12: Shift from baseline in EORTC QLQ-C30 pain scores by treatment and timepoint (October 2023 DCO)

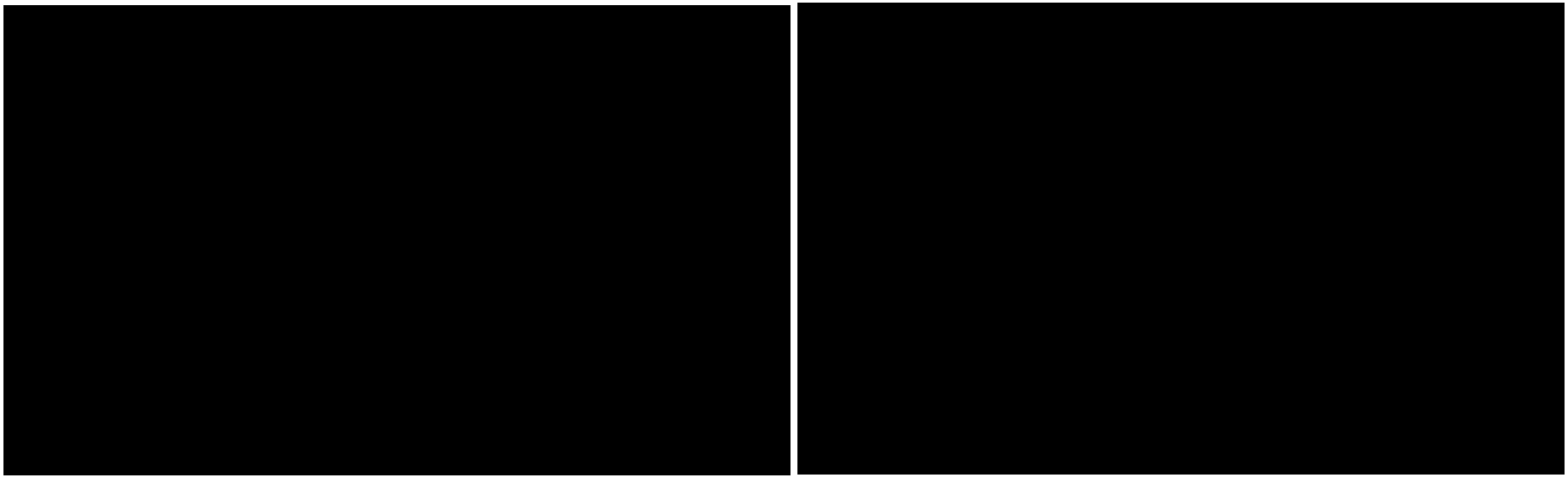


Footnotes: Arm A = SOC and Arm B = liso-cel.
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Changes in HRQoL from baseline for liso-cel versus SOC for physical functioning domain

A summary of the change from baseline in EORTC QLQ-C30 physical functioning scores and the mean change from baseline for patients in the liso-cel and SOC arms at different timepoints are presented in Figure 13.

Figure 13: Shift from baseline in EORTC QLQ-C30 physical functioning scores by treatment and timepoint (October 2023 DCO)

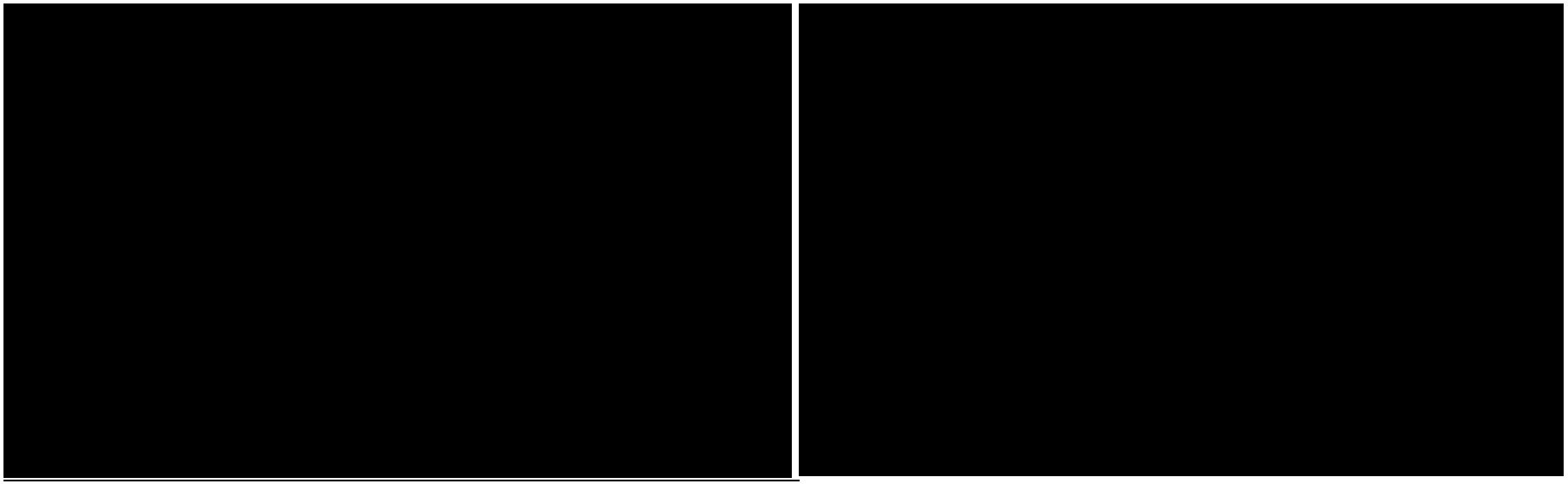


Footnotes: Arm A = SOC and Arm B = liso-cel.
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Changes in HRQoL from baseline for liso-cel versus SOC for cognitive functioning domain

A summary of the change from baseline in EORTC QLQ-C30 cognitive functioning scores and the mean change from baseline for patients in the liso-cel and SOC arms at different timepoints are presented in Figure 14.

Figure 14: Shift from baseline in EORTC QLQ-C30 cogntiive functioning scores by treatment and timepoint (October 2023 DCO)



Footnotes: Arm A = SOC and Arm B = liso-cel.
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

FACT-Lym

Analysis of mean change from baseline of FACT-Lym scores showed similar trends, with the change from baseline in FACT-Lym scores generally higher for SOC compared with liso-cel (Table 21). A summary of the change from baseline in FACT-LymS scores are presented in Figure 15.

The changes from baseline in FACT-Lym scores were clinically meaningfully [redacted] of 3) in the SOC arm after 36 months. In contrast, the change from baseline in the FACT-Lym scores [redacted], suggesting there was a relative improvement in HRQoL for patients who received liso-cel compared with SOC in TRANSFORM. As shown in Figure 15, the FACT-Lym scores deteriorated over time in both the liso-cel and SOC arms (i.e. the mean change from baseline increased), [redacted]. The wide 95% CIs towards the end of the study (i.e. beyond Month 9) were likely due to the small number of patients in both the SOC (n = [redacted]) and liso-cel arms (n = [redacted]).[41]

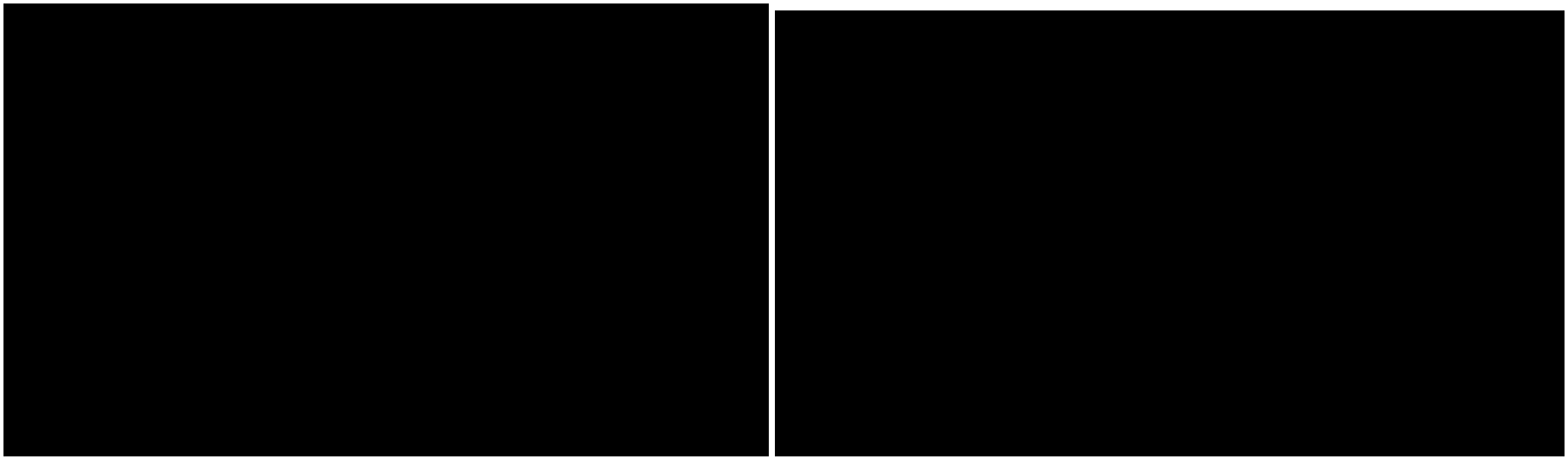
Furthermore, it should be noted HRQoL data were not collected from patients in the SOC arm who crossed over to receive liso-cel and therefore HRQoL results from the SOC arm represent findings for patients who were responding to and/or tolerating SOC treatments well. As such, the negative impact of SOC on HRQoL may have been underestimated in TRANSFORM.

Table 21: Summary of change from baseline in FACT-LymS scores in TRANSFORM (final DCO; October 2023)

PRO	SOC (n=44)						Liso-cel (n=48)					
	# Patients with PRO measure at time point	Baseline value (considering only patients remaining at timepoint)		Value at timepoint		Change from baseline	# Patients with PRO measure at time point	Baseline value (considering only patients remaining at timepoint)		Value at timepoint		Change from baseline
		Value	SD	Value	SD			Value	SD	Value	SD	
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 126	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Baseline is defined as the last PRO assessment on or prior to randomisation
Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; SD: standard deviation; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Figure 15: Shift from baseline in FACT-LymS scores by treatment and timepoint (October 2023 DCO)



Arm A = SOC and Arm B = liso-cel.
Abbreviations: FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma subscale.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

EQ-5D-5L

A summary of the utility scores derived from EQ-5D-5L from TRANSFORM for the overall population (i.e. combining the liso-cel and SOC arms) are summarised in Figure 16 and presented in detail in Table 22. The utility vales for the TRANSFORM population increased over the study period, increasing from [redacted] at baseline to [redacted] at Month 36.[41]

Figure 16: Overall utility scores in TRANSFORM (final DCO; October 2023)

Abbreviations: EOS: end of study.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 22: Overall utility scores in TRANSFORM (final DCO; October 2023)

Visit	N	Mean (SD)	95% CI	Range	Median	IQR
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 126	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36 - EOS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EOS: end of study.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

A summary of the utility scores derived from EQ-5D-5L by treatment arm from TRANSFORM are summarised in Figure 17 and presented in detail in Table 23.

Generally, both treatment arms demonstrated an improvement in utilities over the study duration and utility values were numerically higher for patients in the SOC arm compared with the liso-cel arm throughout. However, similar to the FACT-Lys scores, the 95% CIs overlapped for all timepoints (except month 12), suggesting any differences were not significant. The analyses were also impacted by the small patient numbers in both arms, which introduces uncertainty in the results. In addition, the results may underestimate the negative impact of SOC on HRQoL given only patients who were responding to and/or tolerating SOC treatments were included in the analysis.

Therefore, given the similarity in utility scores, the small patient numbers and the potential bias in favour of the SOC arm, it was not considered appropriate to use treatment-specific utility values to inform the model. Instead utility values for the overall TRANSFORM population were used, separated by event-free and post-event. This data is presented in Table 24 and Table 25.

Figure 17: Utility scores by treatment in TRANSFORM (final DCO; October 2023)

Abbreviations: EOS: end of study; JCAR017: liso-cel; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 23: Utility scores by treatment in TRANSFORM (final DCO; October 2023)

	Liso-cel						SOC					
Visit	**N**	**Mean (SD)**	**95% CI**	**Range**	**Median**	**IQR**	**N**	**Mean (SD)**	**95% CI**	**Range**	**Median**	**IQR**
Baseline	[redacted]											
Day 29	[redacted]											
Day 64	[redacted]											
Day 126	[redacted]											
Month 6	[redacted]											
Month 9	[redacted]											
Month 12	[redacted]											
Month 18	[redacted]											
Month 24	[redacted]											
Month 36 – EOS	[redacted]											

Abbreviations: EOS: end of study; JCAR017: liso-cel; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Figure 18: Utility scores by EFS status in TRANSFORM (final DCO; October 2023)

Abbreviations: EF: event free; EOS: end of study.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 24: Utility scores by EFS status at each visit in TRANSFORM (final DCO; October 2023)

	Event-free (EF)						Post Event-free (Post EF)					
Visit	**N**	**Mean (SD)**	**95% CI**	**Range**	**Median**	**IQR**	**N**	**Mean (SD)**	**95% CI**	**Range**	**Median**	**IQR**
Baseline	[redacted]											
Day 29												
Day 64												
Day 126												
Month 6												
Month 9												
Month 12												
Month 18												
Month 24												
Month 36 - EOS												

Footnotes: Note, EQ-5D values collected post-censoring for EFS were excluded from analyses, since after the censoring date, the pre-EFS or post-EFS state cannot be determined. Therefore, the number of observations is smaller at certain visits (compared with above tables) due to censoring.
Abbreviations: EF: event free; EOS: end of study.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 25: Utility by EFS status – Combined across all post-baseline visits in TRANSFORM (final DCO; October 2023)

EFS Status	N	Mean (SD)	95% CI	Range	Median	IQR
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

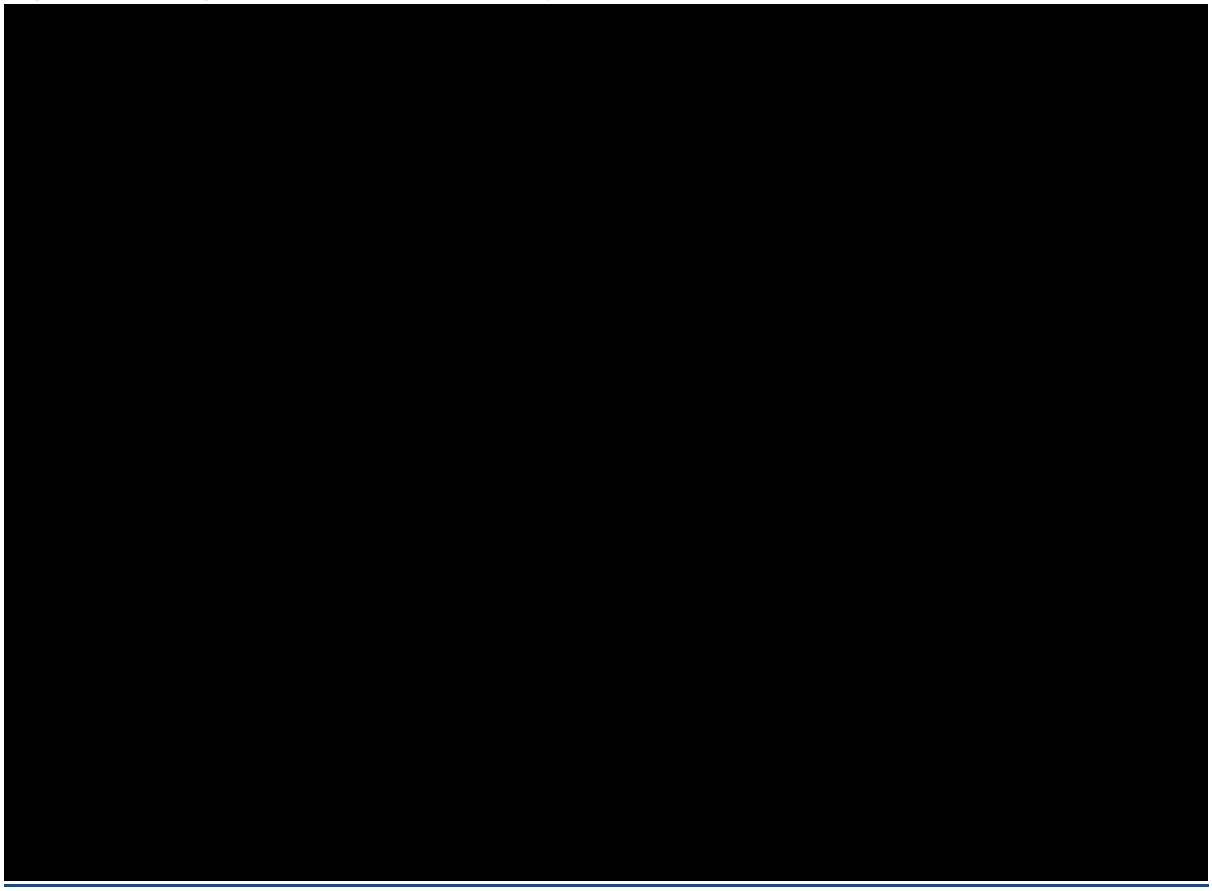
Footnotes: Note, EQ-5D values collected post-censoring for EFS were excluded from analyses, since after the censoring date, the pre-EFS or post-EFS state cannot be determined. Therefore, the number of observations is smaller at certain visits (compared with above tables) due to censoring.
Abbreviations: EF: event free; EOS: end of study.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.7 *Subgroup analysis*

Overall, a consistently superior treatment effect for liso-cel over SOC was observed across subgroups, indicating that the efficacy of liso-cel was generally consistent across the relevant subpopulations enrolled in the trial.[41] In the few subgroups where a significant benefit was not observed (Japanese region and patients with DLBCL transformed from indolent NHL), the lack of statistical significance can be attributed to the small patient numbers in these subgroups and therefore a limited number of events.[41] UK clinicians found this unlikely to impact results and agreed this was likely a chance finding. UK clinical experts also confirmed these results were supportive of a consistent superior treatment effect for liso-cel over SOC across the subgroups and the lack of statistical significance in the few subgroups would not dissuade them from using liso-cel in these patients.[45] A subgroup forest plot of EFS by stratum in the ITT analysis set is presented in Figure 19.

Subgroup analyses for other key secondary endpoints are presented in Appendix M.1.4 and are supportive of a consistent treatment effect for liso-cel across subgroups.

Figure 19: Subgroup forest plot of EFS by stratum



Footnotes: Arm A = SOC arm; Arm B = liso-cel arm.
Abbreviations: ABC, activated B cell; CT, chemotherapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event free survival; HGBCL, high grade B cell lymphoma; GCB, germinal center B cell; IRC, independent review committee; ITT, Intent-to treat; Liso-cel, lisocabtagene maraleucel; NHL: Non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; sAAIPI, secondary age-adjusted International Prognostic Index; SoC: standard of care; SPD, sum of products of diameters.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.8 *Meta-analysis*

The TRANSFORM trial provides a head-to-head comparison between liso-cel and the only relevant comparator in this indication, SOC, and no other trials reporting relevant data on liso-cel in this patient population are available. This section is therefore not applicable as no pooling of trials was required.

B.2.9 *Indirect and mixed treatment comparisons*

The TRANSFORM trial provides a head-to-head comparison between liso-cel and the only relevant comparator in this indication, SOC. Therefore, no indirect treatment comparisons have been conducted and this section is not applicable.

B.2.10 *Adverse reactions*

Treatment emergent adverse events (TEAEs) were defined as AEs occurring or worsening on or after the date of randomisation and within 90 days after last dose of chemotherapy (SOC arm), or within 90 days after the infusion of liso-cel (liso-cel arm or patients in SOC arm crossing over to liso-cel) or start of new antineoplastic therapy, whichever occurred first. All AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[124] AEs observed in the SOC arm were reported prior to patients crossing over to receiving liso-cel therapy. Details of AEs in the post-crossover SOC arm can be found in Appendix M.1.6.

Overall, no new safety concerns were identified in patients with 2L early relapsed/primary refractory LBCL who are eligible for SCT studied in TRANSFORM and the safety events reported in this study were consistent with the known safety profile of liso-cel. The results also demonstrated, as expected, notable differences in regard to adverse events of special interest (AESIs) that are known side effects specific to CAR-T therapy. These events are well-characterised and are mostly mild or moderate in severity; rates of severe CRS and neurological toxicity immune effector cell-associated events (hereafter referred to as neurological toxicity/toxicities) were low (1% and 4%, respectively, with no Grade 4 or 5 events; see Section B.2.10.3).

B.2.10.1 Safety summary

Table 26 presents an overview of the TEAE data up to the final DCO (October 2023). A total of 98.9% of patients in the SOC arm and 100% of patients in the liso-cel arm experienced at least one TEAE during the study. TEAEs of Grade 3/4 occurred in 81 patients (89.0%) who received SOC and 85 patients (92.4%) who received liso-cel. TEAEs leading to withdrawal of any study drug occurred in [redacted] who received liso-cel and [redacted] patients ([redacted]%) who received SOC.[41]

A summary of the deaths occurring in the TRANSFORM trial is presented in Table 27. Overall, 34 patients (37.0%) died in the liso-cel arm, 9 patients (9.9%) died in the SOC arm and 33 patients (56.9%) died in the SOC arm post-crossover. Of these, [redacted] patients in both SOC and liso-cel arms died due to AEs. [redacted] patients died in the SOC arm post-crossover due to AEs.[41]

Table 26: Overall summary of TEAEs, SAS

Category	SOC (n=91) n (%)	Liso-cel (n=92) n (%)
All TEAEs	90 (98.9)	92 (100)
All Grade 3/4 TEAEs	81 (89.0)	85 (92.4)
All TEAEs (related to any drug)	[redacted]	[redacted]
All TESAEs	[redacted]	[redacted]
All TESAEs (related to any drug)	[redacted]	[redacted]
All TEAEs leading to withdrawal of any study drug	[redacted]	[redacted]
All TEAEs leading to dose interruption of any study drug	[redacted]	[redacted]

Abbreviations: AE: adverse event; SAS: safety analysis set; SAE: serious adverse event; SOC: standard of

care; TEAE: treatment emergent adverse event; TESAE: treatment emergent serious adverse event.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Table 27: Overall summary of deaths, SAS

	SOC* (n=91) n (%)	SOC Post-crossover (n=58) n (%)	Liso-cel (n=92) n (%)
Deaths	9 (9.9)	33 (56.9)	34 (37.0)
Causes of death by category			
Death from malignant disease under study, or complication due to malignant disease under study	[redacted]	[redacted]	[redacted]
Death from adverse event (not otherwise specified)	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Patients with treatment emergent AEs leading to death	[redacted]	[redacted]	[redacted]

Footnotes: *SOC arm prior to receiving crossover therapy.
Abbreviations: AE: adverse event; SAS: safety analysis set; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.10.2 Common treatment-emergent adverse events

Table 28 presents the most common TEAEs occurring in ≥ 20% of patients in either treatment group.

The most common TEAEs of any grade in the SOC arm were: thrombocytopenia (66 patients [72.5%]); anaemia (62 patients [68.1%]); nausea (53 patients [58.2%]); neutropenia (50 patients [54.9%]) and diarrhoea ([redacted] patients [redacted%]). Thrombocytopenia, anaemia and neutropenia were also the most common Grade 3/4 TEAEs occurring in the SOC arm, occurring in 62 patients (68.1%), 51 patients (56.0%) and 47 patients (51.6%), respectively.[41]

The most common TEAEs of any grade in the liso-cel group were similar and included: neutropenia (76 patients [82.6%]), anaemia (62 patients [67.4%]), thrombocytopenia (55 patients [59.8%]), nausea (49 patients [53.3%]) and CRS (45 patients [48.9%]). Neutropenia, anaemia and thrombocytopenia were also the most common Grade 3/4 TEAEs occurring in the liso-cel arm, occurring in 75 patients (81.5%), 48 patients (52.2%) and 46 patients (50.0%), respectively.41

Table 28: Incidence of TEAEs occurring in ≥ 20% of patients in either treatment group, SAS

TEAE	SOC (n=91) n (%)		Liso-cel (n=92) n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	66 (72.5)	62 (68.1)	55 (59.8)	46 (50.0)
Anaemia	62 (68.1)	51 (56.0)	62 (67.4)	48 (52.2)
Nausea	53 (58.2)	[redacted]	49 (53.3)	[redacted]
Neutropenia	50 (54.9)	47 (51.6)	76 (82.6)	75 (81.5)

Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	21 (23.1)	[redacted]	40 (43.5)	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	9 (9.9)	[redacted]	24 (26.1)
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	0 (0.0)	[redacted]	45 (48.9)	[redacted]

Abbreviations: TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.10.3 Adverse events of special interest

Table 29 presents an overview of the AESI data up to the final DCO (October 2023).

A total of [redacted]% of patients in the SOC arm and [redacted]% of patients in the liso-cel arm experienced at least one AESI during the study. AESIs of Grade 3/4 occurred in [redacted] patients ([redacted]%) who received liso-cel and [redacted] patients ([redacted]%) who received SOC. AESIs leading to death occurred in [redacted] patient in both study arms.

The most common Grade 3/4 AESIs in the liso-cel group were prolonged cytopenia (40 patients; 43.5%), severe infections (14 patients; 15.2%) and neurological toxicity ([redacted] patients; [redacted]%).

Table 29: Incidence of AESIs in either treatment group, SAS

AESI	SOC (n = 91) n (%)		Liso-cel (n = 92) n (%)	
All AESIs	[redacted]		[redacted]	
All Grade 3/4 AESIs	[redacted]		[redacted]	
All AESIs related to any study drug	[redacted]		[redacted]	
All serious AESIs	[redacted]		[redacted]	
All serious AESIs related to any study drug	[redacted]		[redacted]	
All AESIs leading to death	[redacted]		[redacted]	
All AESIs leading to withdrawal of any study drug	[redacted]		[redacted]	
All AESIs leading to dose interruption of any study drug	[redacted]		[redacted]	
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**
Neurological toxicity	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Cytokine release syndrome	0 (0.0)	0 (0.0)	45 (48.9)	1 (1.1)
Prolonged cytopenia	3 (3.3)	[redacted][a]	40 (43.5)	[redacted][a]
Severe infections	19 (20.9)	[redacted]	14 (15.2)	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]
Infusion Related Reaction (IRR)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Second Primary Malignancy	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Tumour Lysis Syndrome (TLS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Macrophage Activation Syndrome (MAS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]

Footnotes: [a]Based on March 2022 DCO, as breakdown of Grade 3/4 AESIs were not reported in the final DCO (October 2023). There were no changes in any grade AESIs between March 2022 and October 2023 data cuts.
Abbreviations: TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Neurological toxicity immune effector cell-associated events

Table 31 presents the neurological toxic events and the most common symptoms of neurological toxicity (occurring in ≥ 2% of patients) following treatment with liso-cel. Neurological toxicity occurred in 10 patients (10.9%) who received liso-cel, of whom 4 patients (4.3%) had Grade 3 toxicity. No patients in the liso-cel arm of TRANSFORM experienced Grade 4/5 neurological toxicity whereas [redacted] patient ([redacted]) in the SOC arm experienced Grade 4 neurological toxicity. The most common symptoms of neurological toxicity were tremors ([redacted] patients; [redacted]%) and aphasia ([redacted] patients; [redacted]%).

The average duration of neurological toxicity was [redacted] days (standard deviation: [redacted]) and the mean time to the onset of neurological toxicity was [redacted] days (standard deviation: [redacted]) after the infusion of liso-cel.

Table 30: Summary of treatment-emergent neurological toxicity events and symptoms occurring in ≥ 2% of patients, SAS

	Liso-cel (n=92) n (%)
Any neurological toxicity immune effector cell-associated event	10 (10.9)
Overall duration of neurological toxicity event in days (mean, SD)	[redacted]
Time from liso-cel infusion to first neurological toxicity event in days (mean, SD)	[redacted]
Maximum grade	
Grade 1	4 (4.3)
Grade 2	2 (2.2)
Grade 3	4 (4.3)
Grade 4	0 (0.0)
Grade 5	0 (0.0)
Neurological toxicity symptoms by preferred term	
Tremor	[redacted]
Aphasia	[redacted]
Encephalopathy	[redacted]
Dizziness	[redacted]
Headache	[redacted]
Confusional state	[redacted]

Abbreviations: SAS: safety analysis set; SD: standard deviation.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

CRS

CRS is an AE induced by the activated T-cells upon engagement with the CD19 target, so it is considered to be related to treatment with CAR T-cell therapy.[125]

Table 31 presents CRS events and the most common symptoms of CRS (occurring in ≥2% of patients) following treatment with liso-cel. CRS occurred in 45 patients (48.9%) who received liso-cel, of whom 1 (1.1%) had maximum Grade 3 CRS. No patients in TRANSFORM experienced Grade 4/5 CRS. The most common symptoms of CRS were pyrexia ([redacted] patients; [redacted]%), hypotension ([redacted] patients; [redacted]%) and headache ([redacted] patients; [redacted]%).[41]

The average duration of CRS was [redacted] days (SD: [redacted]) and the mean time to the onset of CRS was [redacted] days (standard deviation: [redacted]) after the infusion of liso-cel.[41]

Table 31: Summary of treatment-emergent CRS and CRS symptoms occurring in ≥ 2% of patients, SAS

	Liso-cel (n=92) n (%)
Any CRS event	45 (48.9)

Overall duration of CRS episode in days (mean, SD)	[redacted]
Time from liso-cel infusion to first CRS event in days (mean, SD)	[redacted]
Maximum grade	
Grade 1	34 (37.0)
Grade 2	10 (10.9)
Grade 3	1 (1.1)
Grade 4	0 (0.0)
Grade 5	0 (0.0)
CRS symptoms by preferred term	
Pyrexia	[redacted]
Hypotension	[redacted]
Headache	[redacted]
Dizziness	[redacted]
Tachycardia	[redacted]
Hypoxia	[redacted]
Musculoskeletal pain	[redacted]
Hypertransaminasaemia	[redacted]

Abbreviations: CRS: cytokine release syndrome; SAS: safety analysis set; SD: standard deviation.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Infections

Table 32 presents a summary of the infections and infestations occurring in the SAS of TRANSFORM by treatment, high level group term and high level term. Overall, a similar number of infections and infestations occurred in the liso-cel and SOC arms.

Table 32: Summary of treatment-emergent Adverse Events (TEAEs) for the class of infections and infestations

	SOC (n = 91) n (%)	Liso-cel (n = 92) n (%)
Number of patients with Grade 3 or 4 infections or infestations	19 (20.9)	14 (15.2%)
Infections – pathogen unspecified	[redacted]	[redacted]
Sepsis, bacteraemia, viraemia and fungaemia NEC	[redacted]	[redacted]
Infections NEC	[redacted]	[redacted]
Lower respiratory tract and lung infections	[redacted]	[redacted]
Urinary tract infections	[redacted]	[redacted]
Abdominal and gastrointestinal infections	[redacted]	[redacted]
Dental and oral soft tissue infections	[redacted]	[redacted]
Hepatobiliary and spleen infections	[redacted]	[redacted]

Vascular infections	[redacted]	[redacted]
Bacterial infectious disorders	[redacted]	[redacted]
Escherichia infections	[redacted]	[redacted]
Bacterial infections NEC	[redacted]	[redacted]
Clostridia infections	[redacted]	[redacted]
Enterococcal infections	[redacted]	[redacted]
Klebsiella infections	[redacted]	[redacted]
Pseudomonal infections	[redacted]	[redacted]
Staphylococcal infections	[redacted]	[redacted]
Viral infectious disorders	[redacted]	[redacted]
Coronavirus infections	[redacted]	[redacted]
Caliciviral infections	[redacted]	[redacted]
Herpes viral infections	[redacted]	[redacted]
Fungal infectious disorders	[redacted]	[redacted]
Aspergillus infections	[redacted]	[redacted]
Fungal infections NEC	[redacted]	[redacted]

Footnotes: A patient is counted only once for multiple events within preferred term/high level term/high level group term. AEs were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Abbreviations: NEC: not elsewhere classified.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.2.11 *Ongoing studies*

There are no additional studies planned providing additional clinical evidence for liso-cel in adult patients with LBCL who have relapsed within 12 months, or are primary refractory to 1L immunochemotherapy and are eligible for SCT.

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

B.2.12.1 Principal findings from the clinical evidence base

Liso-cel would address a significant unmet need for LBCL patients with early relapsed/primary refractory disease who are eligible for SCT

As discussed in Section B.1.3.5, there is limited survival benefit associated with current 2L treatments. This is because around 50% of early relapsed/primary refractory patients intended for potentially curative transplant do not receive ASCT for reasons including, but not limited to, inadequate response to re-induction therapy/HDCT or stem cell mobilisation failure.[40, 126] Even for patients who do receive ASCT there is no guarantee of a cure – approximately half of patients treated with ASCT will experience a further relapse and progress to 3L+ treatment.[36-38] As a result, the outcomes for patients with early relapsed/primary refractory LBCL who are eligible for SCT are poor and only an estimated 10% of patients with early relapsed/primary refractory LBCL will be cured with current 2L SOC (Figure 3).[38]

Liso-cel is an innovative, novel and potentially curative treatment option for early relapsed/primary refractory patients at 2L with a high unmet need. CAR-T therapy is currently

only available at 3L+ or later settings in routine UK clinical practice and its introduction has resulted in substantially improved outcomes in this setting and provided potential for cure to patients who previously underwent immunochemotherapy treatments with challenging side effects with little clinical success.[127] Providing CAR-T therapy earlier at 2L may further improve outcomes, including cure rates, compared to 3L+, as 2L patients generally have a lower tumour burden, fewer comorbidities and higher fitness levels. In the TRANSFORM trial, [redacted] patients [redacted] who received 2L CAR-T died due to malignant disease under study or complications, compared to [redacted] patients [redacted] who received 3L+ CAR-T.[41] Earlier access may also result in a proportion of patients being able to receive CAR-T therapy who may otherwise never receive it at 3L+, as a considerable number of patients will die before reaching later lines of therapy, or deterioration in their health will prohibit them from receiving intensive therapies.

The TRANSFORM trial provides a head-to-head comparison between liso-cel and the only relevant comparator in this indication, SOC, and is considered applicable to UK clinical practice

The clinical efficacy and safety evidence base for liso-cel as a treatment for adult patients with DLBCL, HGBCL, PMBCL or FL3B who are eligible for SCT and who are early relapsed/primary refractory to 1L immunochemotherapy is informed by the TRANSFORM trial. In the trial, a total of 184 patients with LBCL (including 118 with DLBCL, 43 with HGBCL, 17 with PMBCL, five with THRBCL and one with FL3B) were included, representing a broad range of LBCL patients.[4] UK clinical experts confirmed that the population included in TRANSFORM is reflective of patients with early relapsed/refractory LBCL in UK clinical practice.[45] Furthermore, the TRANSFORM trial design also reflects UK clinical practice for patients with early relapsed/primary refractory LBCL by allowing patients in the SOC arm to cross over and receive 3L+ CAR-T therapy, mirroring the current real-world treatment pathway. Additionally, TRANSFORM used chemotherapy-based bridging therapy regimens which aligns with the standard approach in the UK to manage disease progression while patients await CAR-T treatment (unlike trials for other CAR-T cell therapies in this indication, for example, ZUMA-7). In addition, with median follow-up of 33.9 months, UK clinical experts considered there was sufficient evidence from the TRANSFORM trial to demonstrate a sustained benefit for liso-cel over SOC across the primary and key secondary endpoints, therefore indicating the data should be considered sufficiently mature for robust decision making.[45]

Treatment with liso-cel leads to an increase in the proportion of patients who are able to receive 2L curative therapy

The potential benefit of liso-cel in improving the number of patients able to receive curative therapy at 2L has been shown in the TRANSFORM trial. Almost two times as many patients randomised to the liso-cel arm received 2L treatment with curative intent, with only 46.7% of patients randomised to SOC in TRANSFORM actually going on to receive HDCT and ASCT following re-induction therapy.[41] In contrast, treatment with liso-cel was received by 96.7% of patients in the liso-cel arm. The TRANSFORM trial supports previous trial observations that only a minority of LBCL patients with early relapsed/primary refractory disease intended for ASCT actually go on to receive ASCT with current 2L SOC, and that the associated overall cure rate in this population remains low.[39, 40]

EFS is the key clinical endpoint for a curative disease such as LBCL and patients in the liso-cel arm of TRANSFORM experienced statistically significant and clinically meaningful improvements in EFS, supported by deeper and more durable responses

The clinical efficacy results from TRANSFORM demonstrate that liso-cel drives clinically meaningful and durable responses and has the potential to cure a greater proportion of patients with LBCL compared to SOC. Results were consistent across the LBCL types presented in this submission (see Section B.2.7) based on data from the final DCO (October 2023), with a median study follow-up of 33.9 months.[41]

The results of the primary endpoint, EFS based on IRC assessment, at the time of the final DCO in TRANSFORM (October 2023), demonstrate that liso-cel is associated with substantial improvements in median EFS compared to SOC (29.5 months versus 2.4 months, respectively). Furthermore, EFS rate at 36 months was 45.8% (95% CI: 35.2, 56.5) in the liso-cel arm compared with 19.1% (95% CI: 11.0, 27.3) in the SOC arm and the stratified HR was 0.375 (95% CI: 0.26, 0.54).[41]

The EFS results from TRANSFORM demonstrate that a substantially larger proportion of patients have the potential to be cured with liso-cel compared to current SOC. Firstly, the correlation between EFS and OS was found to be stronger in DLBCL patients than the correlation between PFS and OS in a large-scale surrogacy analysis based on 30 clinical trials and 47 retrospective studies, demonstrating that EFS is a clinically meaningful endpoint in a curative setting.[128] Secondly, clinical experts estimate that 95% of patients living event-free at two years will achieve long-term remission, and that most patients who would relapse after CAR-T therapy or ASCT would have done so by this two-year timepoint.[5] In addition, a prospective study has demonstrated that patients with DLBCL who were treated with immunochemotherapy and who were living event-free at 2 years had the equivalent OS to that of the age- and sex-matched general population.[129] Applying the estimated 95% long-term remission rates to the two-year EFS rates observed in the TRANSFORM trial suggests that approximately [redacted] of patients will achieve long-term cure following treatment with liso-cel, compared to approximately [redacted] following treatment with SOC. This increase in estimated cure rates for liso-cel of over double that estimates for SOC clearly emphasises the substantial potential benefit of liso-cel in 2L primary refractory/early refractory LBCL.

The secondary endpoints from TRANSFORM provide further evidence of the clinically meaningful treatment benefit provided by liso-cel. At the final DCO (October 2023), ORR was 87% (95% CI: 78.3, 93.1) for liso-cel compared to 48.9% (95% CI: 38.3, 59.6) for SOC.[41] Similarly, 73.9% of the liso-cel arm achieved CR compared to 43.5% of the SOC arm.[41] PFS rate at 36 months was 50.9% versus 26.5% for liso-cel and SOC, respectively.[41]

The curative potential of liso-cel for early relapsed/primary refractory LBCL patients has been demonstrated by the TRANSFORM OS results

The curative potential of liso-cel is supported by the OS results in TRANSFORM; the OS Kaplan-Meier liso-cel curve plateaus at around [redacted] from randomisation, when approximately [redacted] of patients remain alive.[41] OS rate at 36 months was 62.8% versus 51.8%, for liso-cel and SOC, respectively.[41] The stratified OS HR of 0.76 (95% CI: 0.48, 1.19) indicates that liso-cel reduces the risk of death by 24% when compared to SOC; this difference was not statistically significant,

but is confounded by the high proportion (66.3%) of SOC patients who crossed over to receive liso-cel as a subsequent treatment in TRANSFORM.[4, 41]

It is also important to note that the TRANSFORM trial began in October 2018, with the last patient randomised in [redacted].[41] Since the trial began, new 3L+ treatments glofitamab (TA927)[103], loncastuximab tesirine (TA947)[105] and epcoritamab (TA954)[120] have received a positive recommendation from NICE. UK clinical experts indicated that the majority of patients (64.5%) would receive 3L+ treatment with either glofitamab or epcoritamab if they required subsequent treatment following liso-cel.[103, 106] In comparison, [redacted] in the TRANSFORM trial after receiving liso-cel. This means that those patients who are not cured following treatment with liso-cel would be expected to receive more effective 3L+ treatments compared to patients in TRANSFORM who mainly received chemotherapy, and therefore experience improved survival outcomes. In addition, SOC patients in TRANSFORM were apheresed at study entry and so received 3L+ CAR-T on cross-over faster than they would in UK clinical practice, potentially increasing survival for the SOC arm above what would be expected in clinical practice.

The apheresis of T-cells at time of randomisation in the TRANSFORM trial, before being treated with ASCT may also impact the T-cell fitness, potentially improving the ability of T-cells to generate a CAR-mediated immune response to their lymphoma. The CD4:CD8 ratio has been reported as an indicator of T cell fitness, which declines significantly following ablative treatments such as ASCT due to the faster rate of proliferation of CD8 T-cells than CD4 T-cells to reconstitute T-cell composition. A study including patients with R/R multiple myeloma (RRMM) after ASCT by Garfall *et al.* 2019 assessed the impact of disease burden and prior exposure to therapy on the frequency of a memory T-cell subset and CD4:CD8 ratios by comparing the leukapheresis products from patients who underwent leukapheresis prior to first-line ASCT following response to induction therapy and patients with RRMM who underwent leukapheresis for CAR-T BCMA manufacturing.[130] The study found that patients who underwent leukapheresis prior to ASCT had a higher frequency of the memory T-cell subset and significantly higher CD4:CD8 ratios than even patients with RRMM who responded to the CAR-T BCMA treatment.[130] This indicates that patients at earlier lines of treatment (i.e. 2L) exhibit better T-cell fitness and would therefore, likely result in better response compared with 3L+ CAR-T therapy wherein patients would have more heavily R/R disease or have been exposed to prior ablative therapies.[130]

The benefits of moving CAR-T therapy earlier in the treatment pathway are highlighted by the exploratory analyses of TRANSFORM

In TRANSFORM exploratory analyses of patients who crossed-over to 3L+ liso-cel from 2L SOC, patients achieved reduced EFS and response rates compared to patients in the investigational arm of the trial who received 2L liso-cel (median EFS: [redacted] months versus 29.5 months; ORR: [redacted] versus 87.0%; CR: [redacted] versus 73.9%).[41] There is a clear benefit to using CAR-T therapy earlier in the UK treatment pathway as patients are more likely to respond to treatment and derive the subsequent survival benefits compared to the current routine 3L+ setting for CAR-T therapy in the UK.

Liso-cel is well tolerated; AEs associated with treatment can be well-managed

The safety profile observed in TRANSFORM was manageable and generally consistent with the known safety profile of liso-cel reported in TRANSCEND.[16] Rates of any-grade and severe CRS and neurological toxicity were relatively low (48.9% versus 1.1%; neurological toxicity: 10.9% and 4.3%, respectively). Prolonged cytopenias were observed in 43% of patients in the liso-cel arm, and most patients recovered to grade ≤2 within 2 months after infusion. The prolonged cytopenias did not result in a higher rate of severe infections compared with the SOC arm.

In comparison to axi-cel, a CAR-T therapy currently available via the Cancer Drugs Fund (CDF) for 2L early relapsed/primary refractory DLBCL patients and via routine commissioning at 3L+ for DLBCL and PMBCL, liso-cel is shown to be associated with a favourable safety profile. The results of a MAIC between liso-cel and axi-cel, which adjusted for clinically meaningful differences between the TRANSFORM and ZUMA-7 trials, found the MAIC-weighted safety outcomes favoured liso-cel, with lower odds of key CAR-T cell-associated adverse events (AEs) such as CRS and neurological events with liso-cel vs axi-cel.[109] Liso-cel delivers clinically meaningful improvements in patient HRQoL versus SOC

The potential for liso-cel to cure a substantially greater number of patients 2L will in turn result in substantial HRQoL improvements for this early relapsed/refractory LBCL population. By reducing the number of patients experiencing disease progression and the need for further treatments, the introduction of liso-cel would reduce the impact of LBCL symptoms, the psychological burden of having a cancer diagnosis and the side effects of current treatments on HRQoL.

In many HRQoL domains in TRANSFORM, patients in the liso-cel arm reported more favourable HRQoL results compared with those in the SOC arm and low rates of severe CRS (1%) or neurological toxicity (4%) did not appear to affect mean HRQoL outcomes.[41] At the individual level, the proportion of patients with clinically meaningful improvement or no change by Month 6 was higher in patients treated in the liso-cel arm compared with those in the SOC arm across most of the primary HRQoL domains, particularly in global health status/QoL, cognitive functioning and fatigue. The effect of liso-cel compared with SOC on HRQoL may have been underestimated, as patients in the SOC arm who did not respond to treatment could start the next line of therapy, after which HRQoL data were not collected. HRQoL results from the SOC arm therefore represent findings for patients who were responding to and/or tolerating SOC treatments well. In addition, the timing of the HRQoL assessment at Day 126 (i.e. on average 55 days after the date of ASCT) may be too late to capture the negative short-term effect on HRQoL caused by HDCT and ASCT among patients in the SOC arm.

B.2.12.2 Internal/external validity of the clinical evidence base

Internal validity

The clinical evidence base presented as part of the submission has been derived from an SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook. The clinical SLR identified the pivotal clinical trial, TRANSFORM, as the primary evidence source for liso-cel and SOC in the population of interest. The results of the quality assessment of TRANSFORM demonstrated that it is a methodologically robust and well-reported trial, with an overall low risk of bias (Table 13). The Phase III TRANSFORM study of

liso-cel is a large, multicentre trial designed and adequately powered to demonstrate that liso-cel provides superior improvements in EFS compared to SOC.

External validity

The final analyses of TRANSFORM provide almost three years of follow-up (median follow up 33.9 months). As previously mentioned, extensive evidence shows that two years of EFS is strongly correlated with long-term OS, meaning EFS results in TRANSFORM can be used to estimate the proportion of patients likely to achieve cure from treatment.[129]

The TRANSFORM trial and its results are relevant to the decision problem outlined in the NICE scope, specifically the population of interest, which is adult patients with DLBCL, HGBCL, PMBCL or FL3B who are eligible for SCT and who are early relapsed/primary refractory to 1L immunochemotherapy. UK clinical experts confirmed the generalisability of data from TRANSFORM to patients in UK clinical practice.

- **Population:** TRANSFORM provides evidence on the efficacy and safety of liso-cel as a treatment for adult patients with DLBCL, HGBCL, PMBCL or FL3B who are eligible for SCT and who are early relapsed/primary refractory to 1L immunochemotherapy. The population included in the trial is aligned with the expected marketing authorisation for liso-cel in this indication, although represents a subpopulation as only patients eligible for SCT were enrolled. A high proportion of patients enrolled in the TRANSFORM trial were from European countries ([redacted]), with [redacted] from the UK.[114] UK clinical experts confirmed that the population included in TRANSFORM is reflective of patients in the population of interest in UK clinical practice[45]
- **Intervention:** Liso-cel was administered in TRANSFORM in line with how it would be used in UK clinical practice in the population eligible for SCT covered by the anticipated marketing authorisation. Several novel 3L+ treatments are now also available in UK clinical practice,[103, 105, 106] with fewer patients receiving these as a subsequent treatment to liso-cel in TRANSFORM than would be expected in UK clinical practice, potentially underestimating the OS benefits of liso-cel in TRANSFORM.
- **Comparator:** TRANSFORM evaluated the efficacy and safety of liso-cel compared to SOC, which consisted of re-induction therapy followed by HDCT and ASCT. This comparator is consistent with the treatments currently used routinely in UK clinical practice, based on feedback from UK-based clinicians. However, UK clinical experts noted the proportion of patients in the SOC arm requiring subsequent treatment who received subsequent CAR-T therapy in TRANSFORM ([redacted]93.85%) is higher than the estimated corresponding proportion in UK clinical practice (66.25%).[41] Additionally, in UK clinical practice patients would undergo apheresis and CAR-T manufacture only after progression on 2L treatment and therefore would be exposed to 2L immunochemotherapy, HDCT and ASCT. In contrast, in the TRANSFORM trial, patients were apheresed before randomisation and therefore had only received one line of systemic treatment, potentially leading to increased T-cell fitness compared to patients who are apheresed in the 3L setting. Furthermore, apheresis prior to randomisation also ensured there was a median of just [redacted] between 2L progression and receipt of 3L+ CAR-T. There would therefore be a greater delay between progression on 2L treatment and subsequent receipt of 3L+ CAR-T in UK clinical practice compared to the [redacted]

period seen in TRANSFORM trial. All of these factors results in a relative overestimation of OS for the SOC arm, as more patients were able to receive CAR-T without the delay seen in clinical practice that would have a negative impact on OS. The overestimation of OS for patients who received SOC would result in the underestimation of incremental QALYs for patients who received liso-cel.

- **Outcomes:** A range of endpoints were evaluated in TRANSFORM, including those outlined in the NICE scope, that are relevant to patients and clinicians. Where relevant, outcomes were assessed by IRC, which is generally considered to be more robust. The primary endpoint of EFS is an established endpoint in curative settings, which only classes patients with CR or PR as having EFS, rather than also including SD as with PFS. SD is not an acceptable outcome given LBCL is a curative disease, where patients with SD or progression to current treatment would be moved onto a new therapy with potential for cure. Using EFS in appraisals of potentially curative treatment has previously been deemed appropriate for decision making.[5] In addition, as previously mentioned, the correlation between EFS and OS was found to be stronger in DLBCL patients than the correlation between PFS and OS in a large-scale surrogacy analysis based on 30 clinical trials and 47 retrospective studies[128]
- **Study design:** Finally, the design of the TRANSFORM trial closely mirrors UK clinical practice in the treatment of relapsed or refractory large B-cell lymphoma (LBCL) and was considered a well-designed trial by UK clinical experts.[45] Primarily this was because TRANSFORM allowed patients to crossover from the SOC arm to receive 3L+ CAR-T therapy, which aligns with clinical practice in the UK where patients with LBCL who have failed two or more lines of therapy would be eligible for CAR-T treatment. This crossover design ensures that the trial closely resembles the treatment pathway that patients would follow in the UK. Secondly, the TRANSFORM trial used chemotherapy-based bridging therapy regimens, which UK clinical experts agreed were in line with the regimens that would be received in UK clinical practice.[45]

B.2.12.3 Conclusions

The TRANSFORM trial is a methodologically robust study, with a design that closely aligns with UK clinical practice, that demonstrates the efficacy and safety of liso-cel in patients with early relapsed or primary refractory LBCL. Results from the TRANSFORM trial show that liso-cel drives clinically meaningful and durable responses and has the potential to cure a substantially higher proportion of patients versus SOC in patients with early relapsed/primary refractory LBCL, driving improvements in HRQoL alongside a manageable safety profile. Liso-cel would therefore represent a step change in the current treatment paradigm for patients with 2L early relapsed/primary refractory LBCL who are eligible for SCT, and would bring the benefits of CAR-T cell therapy forwards in the UK treatment pathway, providing access to a curative treatment option for a greater proportion of patients.

B.3 Cost effectiveness

Summary of cost-effectiveness

- A cost-utility model was developed to estimate the cost-effectiveness of liso-cel versus SOC, the only relevant comparator (Section B.1.1), for the treatment of adult patients with early relapsed/primary refractory LBCL who are eligible for SCT.
- The model was a partitioned survival model consisting of three mutually exclusive health states: (i) event-free (EF), (ii) post-event (PE), and (iii) death. This analysis was consistent with the NICE reference case and took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% in the base case and a lifetime time horizon was adopted.
- Baseline characteristics were informed by the TRANSFORM trial. Clinical expert feedback confirmed that the two treatment arms were well balanced, and broadly reflective of clinical practice in England.[45]
- Extrapolation of EFS, OS and TTNT for liso-cel and SOC was performed using patient-level data from the TRANSFORM trial and mixture-cure models were used for both liso-cel and SOC. All extrapolations generated similar estimates of both EFS, TTNT and OS, reflecting the robustness of the extrapolations and low uncertainty associated with the choice of curve.
- However, as previously detailed in Section B.2.12, the TRANSFORM trial likely overestimates OS for SOC, and underestimates OS for liso-cel, based on current UK clinical practice – this means that the modelled OS extrapolations for liso-cel and SOC are likely to underestimate the true magnitude of benefit associated with liso-cel
- Health state utility values were derived from the TRANSFORM trial and were assumed to return to age- and gender-matched general population utility values for patients remaining in the event-free health state after 5 years. AE disutilities were informed by previous NICE appraisals and the TRANSFORM trial.
- For liso-cel, a CAR-T tariff cost of £41,101 was applied and assumed to include all costs of care from the decision for a person to have CAR-T therapy to 100 days after infusion, excluding CAR-T acquisition costs, bridging therapy costs, and any costs associated with the treatment of hypogammaglobulinemia (with IVIg), which were costed separately.
- The costs of SOC treatment were based on the drug acquisition and administration costs and adverse event costs associated with the respective re-induction immunochemotherapies as well as HDCT and ASCT.
- Additional costs included subsequent therapies, based on those received in the TRANSFORM trial, the costs associated with follow-up resource and monitoring based on UK clinical expert feedback, and the costs of end-of-life care. Any patients still alive after 5 years were not assumed to receive end-of-life care costs.

Base case cost-effectiveness results

- In the base case deterministic analysis, liso-cel at PAS price was associated with a substantial increase in QALYs gained ([redacted]) versus SOC, at reduced total costs ([redacted]). Therefore, liso-cel at PAS price was dominant versus SOC. In the base case, all other treatments were modelled at list price, including all subsequent treatments.

- In the PSA, considering the combined parameter uncertainty in the model, the ICER for liso-cel versus SOC were seen to be in line with the deterministic base case (dominant), indicating low parameter uncertainty.
- The DSA results identified a small number of key influential parameters, including the proportion of patients receiving subsequent treatment in the SOC arm, and the proportion of patients receiving axi-cel; overall the model was robust to uncertainty in the majority of parameters.
- By providing a substantial increase in QALYs gained at reduced total costs, liso-cel at PAS price is dominant versus SOC and therefore represents a cost-effective use of NHS resources at a WTP threshold of £20–30,000/ QALY.

B.3.1 *Published cost-effectiveness studies*

SLRs were conducted to identify published economic evaluations, HRQoL evidence and health-state utility values (HSUVs) and cost and resource use studies in early relapsed/primary refractory LBCL that may be of relevance to this submission. No restrictions were applied to the transplant-eligibility. Full details of all SLRs (cost-effectiveness, HRQoL and cost/resource use studies) are presented in Appendix G, Appendix H and Appendix I.

The economic SLR was originally conducted on 21st April 2020 with subsequent updates performed on 8th June 2020, 5th February 2021, 2nd May 2022, 1st March 2023 with the most recent update conducted on 1st February 2024.

In total, 198 publications reporting on 167 economic evaluations met the inclusion criteria of the economic SLR. Of the 198 publications, 81 publications reporting on 64 unique studies reported data on 2L patients with early relapsed/primary refractory LBCL and were further considered for subsequent data extraction given their relevance to the patient population of this submission. Among the 64 unique studies, 21 were economic evaluations, seven were HTA reports and 36 were costing studies.

Of the identified studies, only two HTA reports which were previous NICE TAs in R/R DLBCL (TA895 and TA649) were performed from a UK perspective. These include:

- TA649: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma[102]
- TA895: Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line immunochemotherapy[5]

Additional searches of the NICE website also identified one previous TA in R/R DLBCL (TA559/TA872), as listed below:

- TA559/872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies[104, 127]

Modelling approaches for TA649, TA559/872 and TA805 have been summarised in Table 33 and were used as a basis to inform the economic modelling features (e.g. approach, inputs and assumptions) of the current submission.

All other studies identified in the economic SLR were not performed from a UK perspective and therefore not considered relevant to the appraisal. These studies are detailed in Appendix G.

B.3.2 *Economic analysis*

As no relevant economic evaluations comparing liso-cel with SOC in 2L patients with early relapsed/primary refractory LBCL from a UK perspective were identified in the SLR, a *de novo* cost-utility analysis of liso-cel versus SOC relevant to the decision problem for this submission was performed.

The objective of this economic evaluation was to assess the cost-effectiveness of liso-cel as a 2L treatment versus re-induction immunochemotherapy followed by HDCT and ASCT (referred to as SOC) in adult patients with early relapsed/ primary refractory LBCL who are eligible for SCT in UK clinical practice. The population included in the base case economic analysis is considered to be relevant to clinical practice within the NHS and reflects the anticipated positioning of liso-cel in the treatment pathway, as confirmed by UK clinical experts.[45] In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon (equivalent to 50 years) with the discount rate set to 3.5% for both costs and benefits.[131]

The economic evaluation was performed then line with the NICE reference case:

- Health outcomes were measured both in terms of life years gained (LYGs) and quality-adjusted life years (QALYs) gained
- The primary outcome measure for the economic evaluation was the incremental cost-effectiveness ratio (ICER; cost per QALY gained) when liso-cel was compared with SOC
- Clinical effectiveness for liso-cel and SOC was measured through OS and EFS outcomes (see Section B.3.3)

All relevant costs were considered including treatment acquisition costs, administration costs, CAR-T costs, SCT costs, monitoring costs, AE management costs and end-of-life costs (see Section B.3.5).

B.3.2.1 Patient population

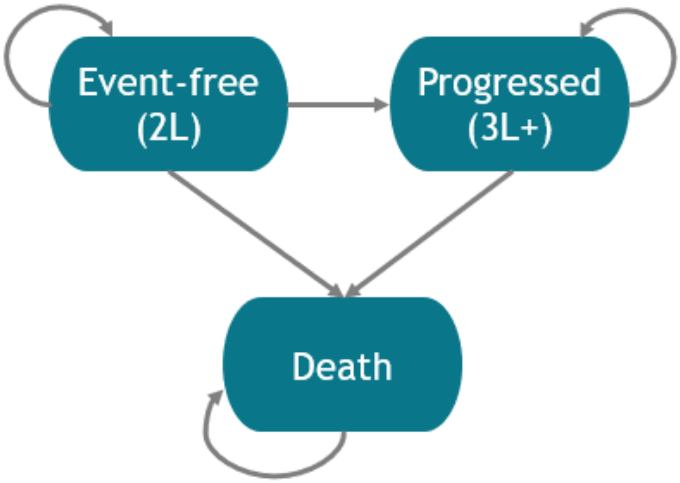
The patient population for the economic evaluation was adult patients with early relapsed /primary refractory LBCL who are eligible for SCT. This is in line with the decision problem for this submission and represents a subpopulation of the anticipated marketing authorisation for liso-cel in this indication, as outlined in Section B.1.3.1.[132] This population also corresponds with the patient population evaluated in the TRANSFORM trial, which provides the clinical evidence base for liso-cel and SOC treatments for adult patients with early relapsed/primary refractory LBCL who are eligible for SCT. In England, patients who have failed first line treatment are currently treated with ASCT if they are eligible and have a limited chance of cure and poor survival outcomes with current SOC; liso-cel could therefore provide a substantial clinical benefit for these patients.

B.3.2.2 Model structure

A *de novo* economic model was developed in Microsoft Excel®. The model structure was based on previous NICE submissions for R/R LBCL,[5, 104, 127, 133, 134] the treatment pathway of patients with early relapsed/primary refractory LBCL who are eligible for SCT, data availability from TRANSFORM and feedback from UK clinical and health economic experts.[5, 41, 104] A partitioned survival model (PSM) was developed, which included three health states (Figure 20):

- Event-free (2L): patients who are alive and event-free
- Post-event (3L+): patients who are alive and have experienced an event
- Death: patients who have died

Figure 20: PSM structure



Abbreviations: 2L: second-line; 3L+: third-line and beyond; PSM: partitioned survival model.

The choice to capture EFS in the model structure rather than PFS was driven by several factors. EFS is the primary endpoint of the TRANSFORM trial (for which the trial is powered) and is defined as the time from randomisation to progressive disease, failure to achieve CR or PR by 9 weeks post-randomisation, or start of a new antineoplastic therapy due to efficacy concerns or death from any cause, whichever occurs first.[41] As outlined in Table 1, Section B.2.6.2 and Section B.2.12.2, EFS is a more clinically relevant endpoint for LBCL than PFS, given the curative intent of treatment. As highlighted by UK clinical experts, it is common practice in LBCL to move patients to the next line of therapy in this setting if their best response is SD, given the severe nature of the condition.[45] Clinical experts agreed EFS is a more clinically relevant endpoint and should be used to inform the economic model.[45]

Furthermore, the use of PFS would be biased by informative censoring. In the TRANSFORM trial, patients randomised to SOC who subsequently switched to liso-cel before disease progression were censored from the PFS analysis.[118] The use of PFS is biased given that the initiation of liso-cel is not random and is related to the patient's perceived eligibility to CAR-T therapy. PFS outcomes would therefore be based on a selection population that was considered to have a better prognosis and more likely to be eligible for liso-cel. This is supported by the

observation of heavier censoring for PFS than EFS in the TRANSFORM trial due to the high proportion of patients who crossed over to liso-cel.

There is also precedent for the use of EFS as an outcome on which to base a PSM. The modelling approach for TA895 (axi-cel for treating R/R DLBCL after first-line immunochemotherapy) used EFS for the same reasons as detailed previously, and this approach was deemed appropriate for decision making.[5, 133]

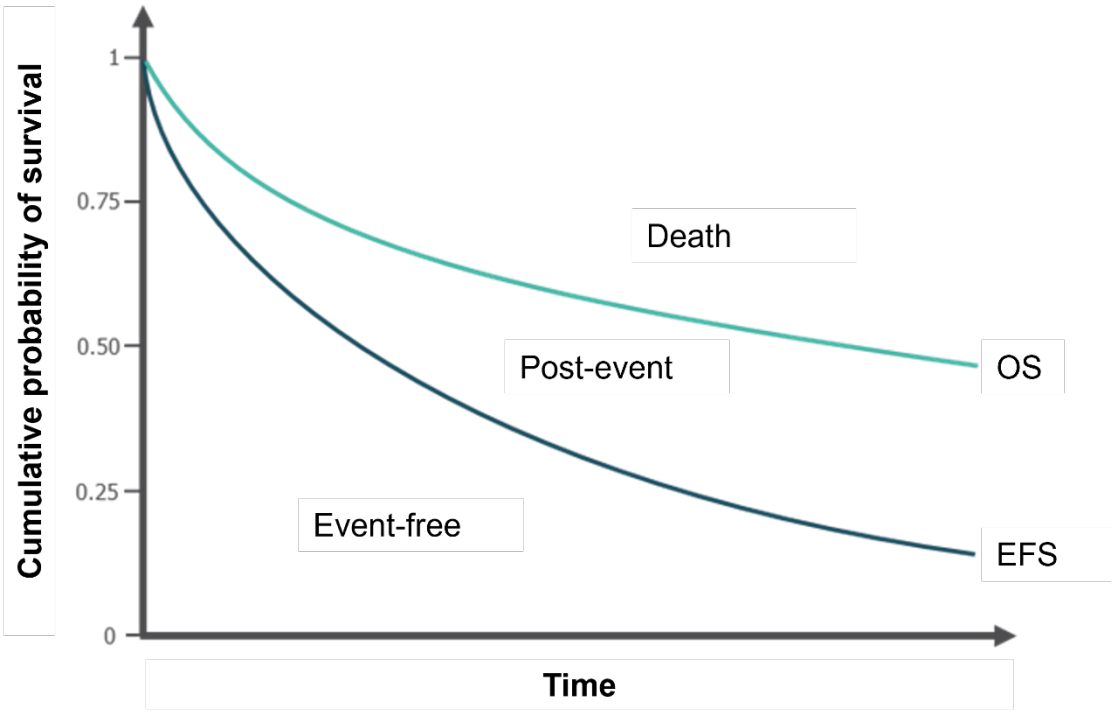
Justification for choice of partitioned survival model

The PSM approach was selected as it allows the clinical benefits of liso-cel to be captured over time through the intuitive incorporation of EFS and OS data, which are key outcomes in both LBCL and the TRANSFORM trial. By modelling OS and EFS based on study-observed events, the model facilitates the replication of within-trial data and is expected to accurately reflect disease progression and the observed survival profile of patients treated with liso-cel and comparator therapies. Unlike state transition models, the PSM model structure does not allow for patients to improve their health state, which reflects the progressive nature of LBCL. Furthermore, the PSM appropriately captures events and long-term extrapolations in a way that allows them to be validated by clinical experts, thereby ensuring the external validity of the outputs of the model. The model's design takes into account the time-dependent nature of the underlying risks, enabling a straightforward integration of a cure component. This structure also allows for the investigation of clinical uncertainties, such as the proportion of patients cured and the potential outcomes for patients following cure, through scenario analyses using alternative extrapolations.

The use of a PSM also aligns with previous NICE evaluations in R/R LBCL and is the most widely accepted model in oncology by HTA bodies.[5, 102, 106, 127, 135] In both prior CAR-T therapy appraisals in LBCL, the committee accepted the model structure as appropriate for decision making.[5, 127]

The proportion of patients within each health state was determined by OS and EFS curves via an area-under the curve approach (Figure 21). The EFS curve determined the proportion of patients remaining alive and event-free (2L) and the OS curve determined the proportion of patients remaining alive (regardless of event status) and proportion of patients occupying the death health state (calculated as 1 – OS curve). The difference between the EFS and OS curves determined the proportion of patients remaining alive post-event (3L+). The PSM model therefore models the clinical benefits of liso-cel by reflecting the proportion of patients expected to be alive and/or event-free over time.

Figure 21: Determination of state membership in a standard three-state PSM



Abbreviations: EFS: event-free survival; OS: overall survival; PSM: partitioned survival model.

A potential limitation of the PSM structure includes the lack of an explicit link between EFS and OS, as each outcome is modelled independently. This could lead to incongruent relationships of EFS and OS (e.g. the EFS and OS curves crossing). However, in this model, the curves produce plausible estimates and EFS is capped by OS to prevent any logical inconsistencies. Therefore the PSM is considered appropriate to model the occupancy of the event-free, post-event and death health states.

Another limitation of a PSM is the structure only includes one post-event state which can limit how subsequent treatment costs are applied. In a state transition model (STM), separate health states could be included for each subsequent treatment line allowing for more accurate costing of treatments at each line. In this instance, the model includes a single application of subsequent treatment costs, per the approach in TA895, and therefore a PSM was considered appropriate.[5] In the model, the cost of subsequent therapy was applied on as a single one-off cost for patients in the post-event health state based on TTNT data from the TRANSFORM trial. This represents a simplifying assumption, which aims at applying subsequent treatment costs on a time-dependent basis, as the time spent in the post-event health state is not easily able to be tracked within the cost-effectiveness model (CEM). As the duration of subsequent treatment is generally less than a year, this simplifying assumption is expected to have a negligible impact on the modelled results.

Features of the economic analysis

Of the three evaluations identified in Section B.3.1, the two previous NICE evaluations for CAR-T therapies in this indication were considered most relevant for this appraisal: R/R LBCL: TA559 (axi-cel for treating DLBCL and PMBCL after two or more systemic therapies) and TA895 (axi-cel for treating R/R DLBCL after first-line immunochemotherapy).[5, 127] Both evaluations used a three-

state PSM and adopted a lifetime horizon. A summary of the key features of the economic analysis compared with these previous appraisals, as well as TA649 also identified in Section B.3.1 is presented in Table 33.

Perspective

In line with the NICE reference case, the analysis was undertaken from a UK NHS and PSS perspective.[136]

Cycle length

The model used a weekly cycle for the first five years, followed by an annual cycle. The weekly cycle captures the costs and utility variation associated with high event rates in the first five years. Post Year 5, the health state occupation in the model will have stabilised and therefore less granular modelling of costs/utilities could be applied. Previous models used in NICE evaluations for CAR-T therapies in R/R LBCL used cycle lengths of one month across the model time horizon.[5, 127] Given the stabilisation of health state occupation post Year 5, an annual cycle length was preferred to increase computational efficacy without compromising accuracy.

Half cycle correction was included in the economic model. This helps to reduce systemic over/underestimation of costs and other outcomes, and is in line with the recommended best practice.[137]

Time horizon and discounting

The costs and outcomes in the model were calculated over a lifetime horizon. Considering a mean age at model entry of [redacted] years, a time horizon of 50 years was used in the base case to represent a lifetime horizon; 0% of patients are expected to be alive in the model at the end of the time horizon. This is in line with the NICE reference case and based on the NICE guideline recommendation 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 that are being compared.[136] This is also consistent with the approach taken in previous models used in NICE evaluations for CAR-T therapies in R/R LBCL.[5, 127]

Both costs and effects were discounted at 3.5% per annum in accordance with the NICE reference case.[136]

Table 33: Features of the economic analysis compared to previous NICE evaluations in the population of interest

Factor	Previous evaluations			Current evaluation	
	TA895 (2L axi-cel)[5]	TA559/TA872 (3L+ axi-cel)[127]	TA649 (3L+ Pola+BR)[102]	Chosen values	Justification
Model design	Three-state PSM	Three-state PSM	Three-state PSM	Three-state PSM	Captures the clinical benefits of liso-cel and is aligned with previous NICE evaluations in similar indications
Time horizon	Lifetime (50 years)	Lifetime (44 years)	Lifetime (45 years)	Lifetime (50 years)	In line with NICE reference case[136] and sufficiently long to be considered a lifetime horizon based on patient starting age of [redacted] and sufficient to capture any differences in costs or outcomes between the technologies being compared
Cycle length	1 month	1 month	1 week	1 week for the first 5 years, followed by an annual cycle. Half-cycle correction applied to all costs and outcomes, except for one-off costs (e.g. CAR-T acquisition costs) which are applied at the start of first model cycle	The weekly cycle captures the costs and utility decrements associated with high event rates in the first five years. The annual cycle length in later years is considered suitable for later years given the fewer number of events occurring from Year 5 onwards.
Discount	3.5%	3.5%	3.5%	3.5%	In line with NICE reference case[136]
Health effects measure	QALYs	QALYs	QALYs	QALYs	In line with NICE reference case[136]
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	In line with NICE reference case[136]
Treatment waning effect	No treatment waning applied	No treatment waning applied	No treatment waning applied	No treatment waning applied	CAR-T therapies can be potentially curative for some patients, with data from TRANSFORM suggesting that approximately [redacted] of patients will

					achieve long-term cure following treatment with liso-cel.[41] Therefore, mixture cure modelling is the most appropriate approach to capture this potential for cure, as outlined in Section B.3.3.2 and in line with the precedent set in TA895.[5] The mixture cure modelling approach separates the patient population into those that achieve cure and those who do not. For those who do not achieve cure, they are modelled to experience disease progression and death relatively quickly and the data from the TRANSFORM trial is considered suitable to capture the outcomes for these patients. Appropriate extrapolation distributions were selected such that all patients who did not achieve cure experienced an event or death within a short period of time, aligned with previous estimates provided by clinical experts in TA895 (see Section B.3.3). [5] For those who achieve cure, there is no evidence to suggest these patients would experience a 'waning' of treatment effect over time. A standardised mortality ratio (SMR) of 1.09 was applied to cured patients, in line with other 2L and 3L+ CAR-T LBCL NICE submissions (TA872 and TA895) and clinical validation received as part of this submission, in order to capture the additional risk of mortality for these cured patients.[5, 104] No

					treatment waning assumptions are therefore required.
Source of health state utilities	ZUMA-7 trial EQ-5D-5L data cross walked to EQ-5D-3L values for pre-event states. Utilities from previous NICE appraisals applied for post-event states	ZUMA-1 trial EQ-5D-5L cross walked to EQ-5D-3L values	Utilities were derived from TA559, based on the ZUMA-1 trial.	TRANSFORM trial EQ-5D-5L data cross walked to EQ-5D-3L values using the NICE recommended EEPRU dataset[138]	Health-state utility values were derived from EQ-5D-5L data from TRANSFORM. These utility values were deemed to be the most appropriate for use in the cost-effectiveness model, as per the NICE reference case.[136]
Source of costs	• NHS Reference Costs • PSSRU • BNF • eMIT • Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	• NHS Reference Costs • PSSRU • BNF • eMIT • Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	• NHS Reference Costs • PSSRU • BNF • eMIT • Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	• NHS Reference Costs • PSSRU • BNF • eMIT • Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	In line with the NICE reference case[136] Costs were based on established sources of costs within the NHS and were inflated to 2021/2022 as appropriate.

Abbreviations: BNF: British National Formulary; CAR-T: chimeric antigen receptor T-cell; eMIT: electronic market information tool; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; EQ-5D-5L: EuroQoL-5 dimensions-5 levels; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSM: partitioned survival model; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; TA: technology appraisal.
Source: NICE TA895;[5] NICE TA559.[127]

B.3.2.3 Intervention technology and comparators

Intervention

The intervention included in the model is liso-cel, which is implemented in the model as per the anticipated marketing authorisation, and is reflective of the decision problem described in Section B.1.1. As previously described, this submission focusses on a subpopulation of the marketing authorisation for liso-cel, by only considering patients eligible for SCT.

Liso-cel is an autologous anti-CD19 CAR-T therapy, that recognises and eliminates all CD19 expressing target cells, including B-cell malignancies and normal B-cells.[132] The mechanism of action and process for manufacturing and administering liso-cel is described in Section B.1.3.2. Liso-cel is administered as a single autologous IV infusion.[132] Before infusion with liso-cel, patients are treated with lymphodepleting chemotherapy (LDC) consisting of cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day administered for three days as a pre-treatment; 58/92 (63.0%) of patients in the TRANSFORM trial were also treated with bridging therapy before the start of lymphodepleting chemotherapy.[132]

Patients in the liso-cel arm are separated into patients who do and do not receive liso-cel infusion. Infused patients are modelled to incur the full costs of liso-cel whereas non-infused patients are modelled to incur the costs of leukapheresis and bridging chemotherapy and then may ultimately progress to receive 3L+ treatment. The efficacy evidence informing the liso-cel arm is derived from the ITT population (n=92) from TRANSFORM which included both infused (n=90) and non-infused patients (n=2).[4] Of the 90 infused patients, 89 received liso-cel whilst one patient received a non-conforming product. Costs associated with CAR-T acquisition for patients who received a non-conforming product were not accounted for, although administration costs were included in line with patients receiving liso-cel (see Section B.3.5). Of the two non-infused patients, one patient had withdrawn consent from the study whilst another patient did not receive liso-cel due to manufacturing failure.

Comparators

In line with current SOC in UK clinical practice and the control arm of the TRANSFORM trial, the comparator included in the model is re-induction immunochemotherapy followed by HDCT and ASCT. As described in Section B.1.3.4, patients with early relapsed/primary refractory LBCL who are fit enough to tolerate intensive therapy should be offered 2L re-induction immunochemotherapy with the aim to obtain a sufficient response, harvesting stem cells and consolidation with HDCT and ASCT. As per Section B.1.1, Pola+BR is not considered a relevant comparator for the patient population of interest in this economic analysis given its recommendation in patients not suitable for ASCT.[102]

In TRANSFORM, the re-induction immunochemotherapy regimens received were R-DHAP, R-GDP or, R-ICE followed by HDCT and ASCT in responders.[41] In the base case economic analysis, the distribution of re-induction immunochemotherapy regimens was informed by the TRANSFORM trial;[41] a scenario analysis was explored using alternative estimates based on clinician feedback (see Section B.3.11.3).[5] The clinical experts agreed it is reasonable to assume equal efficacy across all of the platinum-based immunochemotherapy regimens, therefore the distribution of re-induction immunochemotherapy regimens only impacts costs in the CEM.[45] The costs associated with re-induction immunochemotherapy are detailed in Section B.3.5.1.

Based on the TRANSFORM trial, 46.7% of all SOC patients are modelled to go on to receive HDCT and ASCT.[41] The costs associated with HDCT and ASCT are detailed in Section B.3.5.1.

The efficacy evidence for SOC is informed by the ITT population (n=92) of the SOC arm in the TRANSFORM trial.[41] A total of 60 patients in the SOC arm (n=92) received liso-cel as a crossover treatment, of which 57 patients received liso-cel infusion and one patient received a non-conforming product.[41] As axi-cel is approved for routine commissioning as a 3L+ CAR-T treatment in LBCL, patients receiving 3L+ liso-cel as a cross-over treatment in the TRANSFORM trial is reflective of UK clinical practice.[41, 104] In a MAIC conducted by Maloney *et al.* (2021) comparing the efficacy of 3L+ liso-cel (TRANSCEND trial) and 3L+ axi-cel (ZUMA-1 trial), after matching and adjusting for clinically relevant prognostic factors, similar MAIC-weighted efficacy outcomes were reported for PFS and OS with a HR of 0.81 (95% CI: 0.44, 1.49) and 0.95 (95% CI: 0.58, 1.57), respectively.[47] These results support the assumption of equivalence between 3L+ liso-cel and 3L+ axi-cel in the model.

B.3.2.4 Subsequent treatments

Clinical expert feedback indicated that the subsequent treatments received in the TRANSFORM trial, in particular for patients in the liso-cel arm, do not fully reflect UK clinical practice.[45] TRANSFORM was conducted before the routine availability of bispecific antibodies and antibody-drug conjugates, meaning that very few patients received these novel treatments. Across both arms of the TRANSFORM trial, [redacted]. In UK clinical practice, the majority of patients who receive liso-cel at 2L would now receive a 3L+ bispecific or antibody drug conjugate if they require a subsequent treatment as per clinical opinion.[45] However, in TRANSFORM, most patients received chemotherapy following 2L liso-cel.[41, 114] As bispecific antibodies and antibody-drug conjugates have been shown to be more effective than chemotherapy, it is expected that using the TRANSFORM trial to model the outcomes in the liso-cel arm underestimates the OS of patients receiving liso-cel, relative to UK clinical practice.[102, 103, 105, 106] As such, the economic analysis presented is considered a conservative approach.[45]

Furthermore, compared with the liso-cel arm, the impact of the availability of 3L+ bispecific antibodies on the SOC arm is expected to be lower. This is because the majority of patients (61.9%; 57/92 patients) in the SOC arm received 3L+ liso-cel, which is broadly reflective of UK clinical practice wherein patients may receive axi-cel as a 3L+ CAR-T treatment.[41] In fact, clinicians noted that, of the percentage of patients requiring subsequent treatment, a higher proportion of patients in the TRANSFORM trial received 3L+ CAR-T (93.85%) than expected in clinical practice (66.25%), thereby overestimating the OS for the SOC arm.[45]

It was not considered feasible to adjust the TRANSFORM OS data to account for the impact of 3L+ bispecifics in UK clinical practice given the lack of real-world data and the recent availability of these treatments. Therefore, in order to ensure consistency with the modelled OS data, the modelling of subsequent treatments in line with the TRANSFORM trial was considered to represent the most appropriate approach in the base case economic analysis. Modelling the costs but not the efficacy of 3L+ bispecifics would mean that the economic analysis would be heavily biased against liso-cel, which would introduce substantial uncertainty. To explore the impact of this assumption on the cost-effectiveness results, a scenario analysis using clinician estimates (see Table 78) of patients receiving 3L+ treatment, including CAR-T therapy and newly approved treatments such as bispecifics, and the incorporation of TRANSFORM and CORAL

trial efficacy were explored, results of which are presented in Section B.3.11.3. The CORAL trial is a phase III multicentre RCT which compared the efficacy of R-ICE and R-DHAP regimens in R/R DLBCL patients who subsequently received ASCT with or without rituximab maintenance therapy.[39] Additional information on the CORAL trial can be found in Appendix R.

A summary of the subsequent treatment distributions adopted in the base-case economic analysis is provided in Section B.3.5.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The patient baseline characteristics in the model were informed by the final DCO (October 2023) of the TRANSFORM trial (median follow-up 33.9 months) which included a patient population that was in line with the final scope (Section B.1.1).[41] The baseline characteristics were validated by UK clinicians consulted as part of this submission to be representative of patients with early relapsed/primary refractory LBCL who are eligible for SCT in UK clinical practice.[45] A summary of the patient baseline characteristics in the economic model is presented below in Table 34.

Age and sex are included in the model to determine general population mortality and utility inputs. Mean body weight and body surface area (BSA) are included in the model to calculate drug acquisition costs. Section B.2.3.2 provides further details on the baseline characteristics of TRANSFORM and Section B.2.12 discusses the applicability of TRANSFORM evidence to clinical practice.

Table 34: Summary of baseline characteristics used in the economic model

Characteristics	2L patients with early relapsed/primary refractory LBCL eligible for SCT	Source
Mean age, years	[redacted]	TRANSFORM (Total ITT analysis set [N=184])[41]
Proportion of female patients, %	42.9	
Mean body weight, kg	[redacted]	
Mean BSA, m^2	[redacted]	

Footnotes: [a]Based on n=180.
Abbreviations: BSA: body surface area; ITT: intention-to-treat; LBCL: large B-cell lymphoma; SCT: stem-cell transplant.

B.3.3.2 Survival inputs and assumptions

The economic model is a cohort-based PSM consisting of three mutually exclusive health states: event-free (2L), post-event (3L+) and death. The proportion of patients in each health state in each weekly cycle is determined for liso-cel and SOC from cumulative survival probabilities from EFS and OS extrapolations. Time to next treatment (TTNT) was also included in the model to determine the timepoint for initiation of subsequent therapy and the proportion of patients receiving subsequent treatment in both the liso-cel and SOC arms.

As the follow-up period for the TRANSFORM trial was shorter than the model time horizon, extrapolations of the observed EFS, OS and TTNT data were required. Extrapolation of EFS, OS

and TTNT for liso-cel and SOC was therefore performed using patient-level data from the enrolled population of the TRANSFORM trial using the final DCO (October 2023), which corresponded to a median follow-up of 33.9 months.[41] The population included in this analysis was the full ITT population, providing data for 92 patients in the liso-cel arm and 92 patients in the SOC arm. Standard parametric distributions and mixture cure models were fitted to each arm of the trial data for EFS, OS and TTNT. Mixture cure models are described in this section as they were considered more appropriate, while the standard parametric models are reported in Appendix N.

Mixture cure models

Mixture cure models represent an appropriate approach to the modelling of survival with cancer therapies which account for more complex hazard functions whereby a proportion of patients have more favourable outcomes (i.e., experience cure and are long-term survivors) following treatment, and a proportion do not. They estimate the probability that patients experience a 'statistical cure' (referred to as the 'cure fraction'), and apply this cure fraction to split the TRANSFORM population into two groups: patients who experience a 'statistical cure' and those who do not. Mortality for 'statistically cured' (hereafter known as 'cured') patients is captured by standardised mortality ratio (SMR)-adjusted age- and gender-matched general population mortality data (derived from UK life tables for 2018–2020).[139] Mortality and risk of progression for 'non-cured' patients is defined by the standard parametric survival model fits to TRANSFORM data. Full details of the methodology for extrapolating clinical trial results using mixture cure models is provided in Appendix O.

Justification for mixture cure models

For reference, the KM data for EFS, OS and TTNT for both liso-cel and SOC based on the final DCO (October 2023) are presented in Figure 22, Figure 24 and Figure 26, respectively. KM data for EFS and OS based on the primary analysis (May 2022 DCO), which informed the marketing authorisation, are presented in Figure 23 and Figure 25, respectively. KM data for TTNT based on the May 2022 DCO did not inform the marketing authorisation and therefore, have not been presented below. A clear plateau is observed for EFS at approximately 16 months from randomisation for liso-cel and 12 months for SOC, in both the final and primary data cuts. Similarly for OS, in Figure 24, a clear plateau is observed at approximately 30 months for both liso-cel and SOC. Finally, for TTNT, in Figure 26, a clear plateau is observed at approximately 16 months from randomisation for liso-cel and 12 months for SOC.

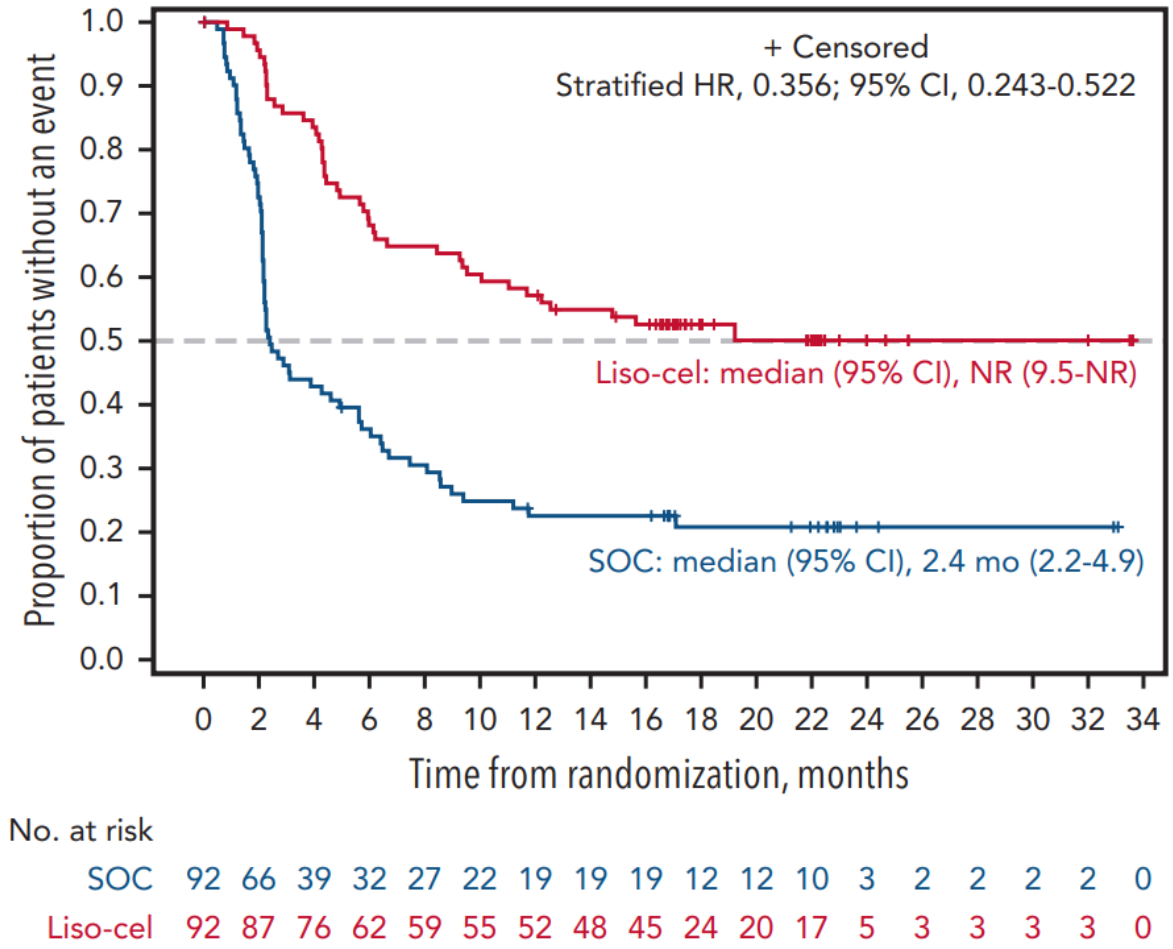
The plateaus observed in the EFS, OS and TTNT data suggest that a proportion of patients with early relapsed/primary refractory LBCL experience long-term remission and survival. Similar results were also observed in the KM data of both PFS and OS for liso-cel in TRANSCEND and for axi-cel in ZUMA-1 and JULIET, suggesting that a proportion of patients achieved long-term remission. The results from these trials supports the use of mixture cure models, as described in TSD 21, to model the long-term outcomes of patients with early relapsed/primary refractory LBCL who respond to CAR-T cell therapy.[140] As highlighted in Appendix N, standard parametric models were not considered suitable to model long-term EFS, OS and TTNT in this indication as they underestimate outcomes for this patient population and are unable to adequately capture the complex hazard function associated with the potential for cure. As described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21, when extrapolating clinical trial data to estimate lifetime outcomes, standard parametric models are limited with respect to the type of hazards they can represent.[140]

The use of MCMs has also been deemed appropriate in past NICE CAR-T appraisals such as TA895 and TA872 in R/R DLBCL and TA554 in R/R ALL whereby patients who survive beyond five years were considered to be effectively cured.[5, 104, 133] In TA895, the EAG considered the use of mixture cure models to be "an appropriate approach that allows for the estimation of more complex hazard functions."[5] Moreover, a retrospective comparison of survival projections for CAR-T therapies in LBCL demonstrated that, together with cubic spline models, mixture cure models provide the most accurate survival extrapolations of CAR T-cell therapies in LBCL.[141] Furthermore, as noted in TA895, a validation study by Vadgama *et al.* (2022) of survival models using follow-up data of five years from the ZUMA-1 trial found that the mixture cure models most accurately and reliably predicted the long-term survival for DLBCL patients treated with axi-cel.[5, 142] Therefore, the use of mixture cure models was considered appropriate to model the EFS and OS data for liso-cel in patients with early relapsed/primary refractory LBCL in this submission. This approach was also validated by UK clinical and health economic experts, who agreed mixture cure models were appropriate in this indication.[45]

Figure 22: Kaplan-Meier plot for EFS based on IRC assessment, ITT (October 2023 DCO)

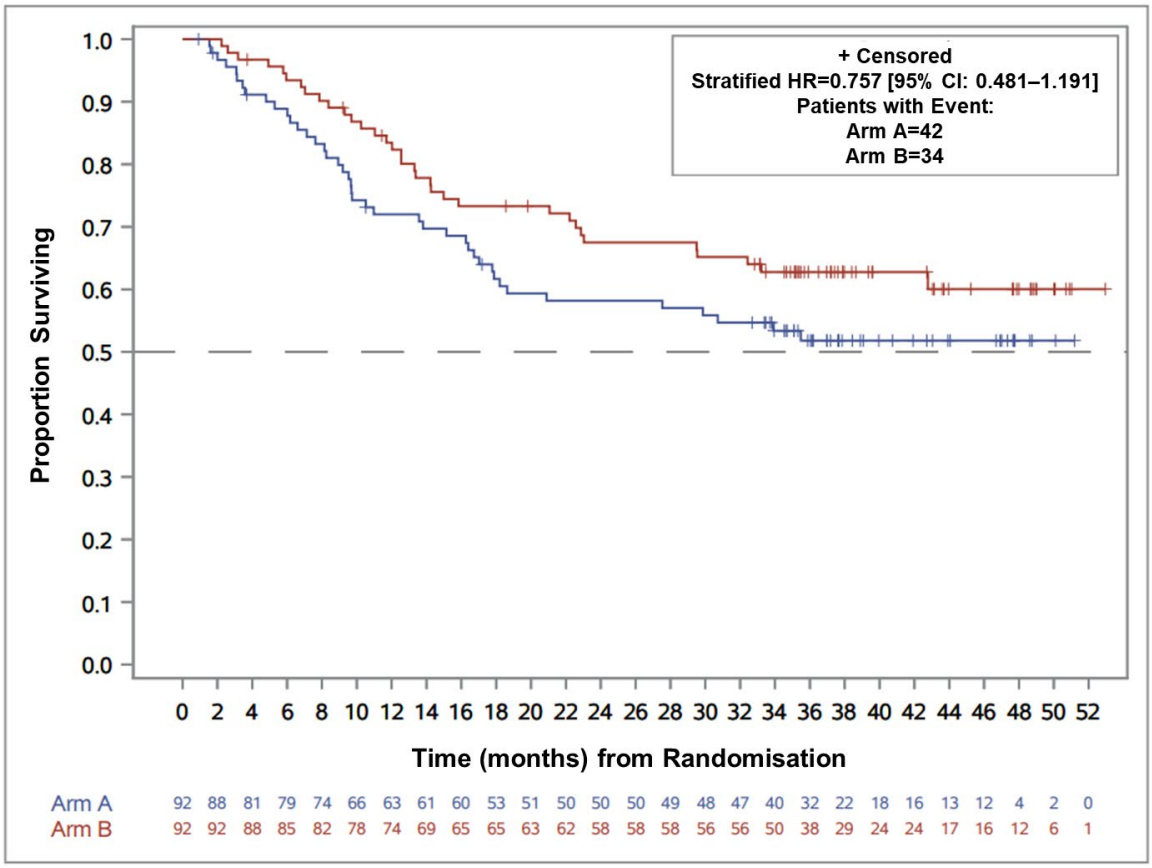
Footnotes: Arm A = SOC arm; Arm B = liso-cel arm
Abbreviations: CI: confidence interval; EFS: event free survival; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Figure 23: Kaplan-Meier plot for EFS based on IRC assessment, ITT (May 2022 DCO)



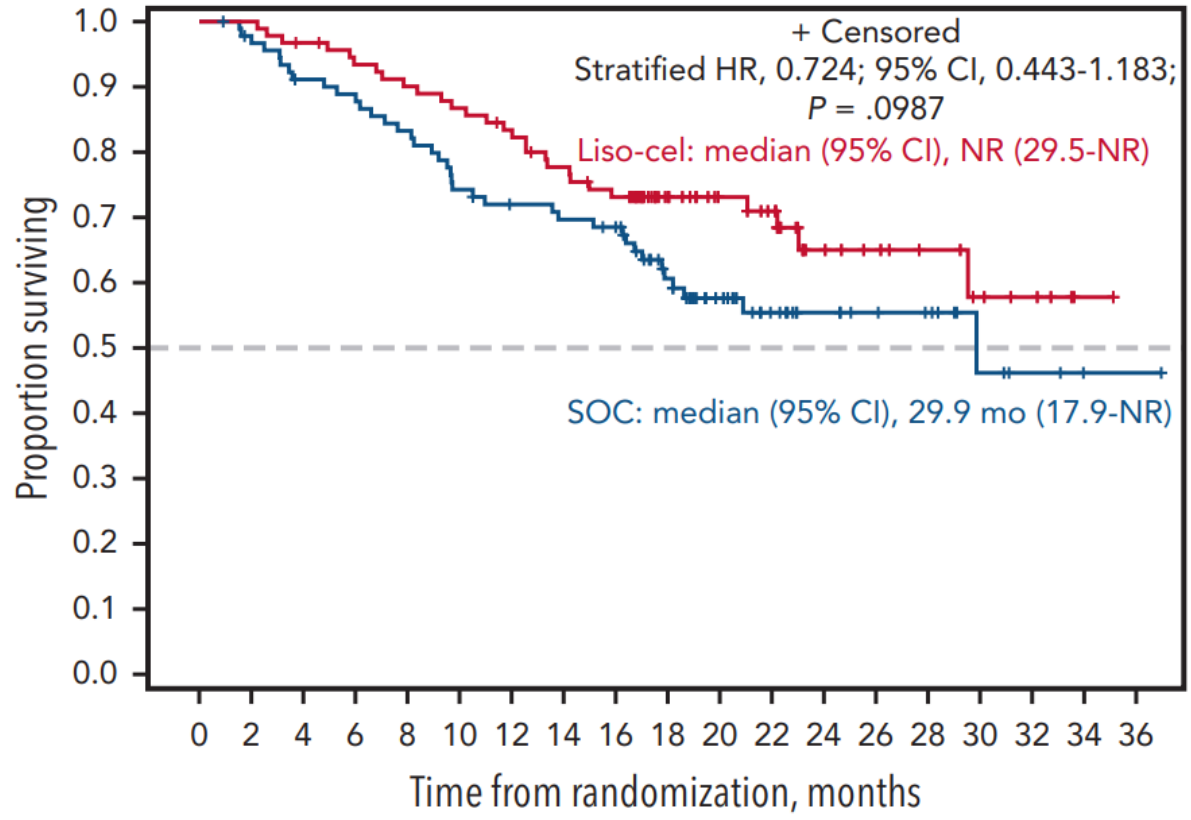
Abbreviations: CI: confidence interval; DCO: data cut-off; EFS: event free survival; HR: hazard ratio; IRC: independent review committee; ITT: intention-to-treat; NR: not reached; SOC: standard of care.
Source: Abramson *et al.* (2023).[4]

Figure 24: Kaplan-Meier plot for OS, ITT (October 2023 DCO)



Footnotes: Arm A = SOC arm; Arm B = liso-cel arm
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival.
Sources: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Figure 25: Kaplan-Meier plot for OS, ITT (May 2022 DCO)



No. at risk

SOC	92	88	81	79	74	66	62	60	58	41	30	21	15	12	10	5	3	1	1
Liso-cel	92	92	88	84	81	78	74	68	63	43	34	30	16	13	10	7	5	1	0

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; OS: overall survival; SOC: standard of care.
Source: Abramson *et al.* (2023).[4]

Figure 26: Kaplan-Meier plot for TTNT, ITT (October 2023 DCO)

Abbreviations: CI: confidence interval; DCO; data cut-off; HR: hazard ratio; ITT: intention-to-treat; KM: Kaplan–Meier; SOC: standard of care; TTNT: time to next treatment.

Mixture cure models were fitted to EFS, OS and TTNT data from the TRANSFORM trial in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14 and 21.[140, 143] The full range of parametric distributions were explored (exponential, Weibull, log-logistic, log-normal, Gompertz, gamma and generalised gamma). The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were estimated for each parametric function.

Log-cumulative hazard plots and Schoenfeld residuals for EFS and OS from TRANSFORM are reported in Appendix P.

For EFS, the proportional hazards assumption was shown to be violated based on the global Schoenfeld test, meaning that the use of independent models fitted separately for EFS for liso-cel and SOC was considered to represent the most appropriate methodology, in line with the curve selection guidance provided in NICE TSD14.[143]The violation of the PH assumption is highly expected, given the different mechanism of actions associated with liso-cel compared with SOC, and the use of independent models allows the changing hazard profile over time to be most accurately captured for both treatments.

Proportional hazards assessment was not available for TTNT at the time of submission. However, given the similarity between the EFS and TTNT results (as a large proportion of EFS events are also TTNT events), it is likely the proportional hazards assumption would also be violated for TTNT and therefore independent survival models for TTNT for liso-cel and SOC were fitted.

Unlike EFS, for OS, based on the observed trial data, the proportional hazard assumption was not violated. This is likely to be the result of the high proportion of patients who crossover to receive liso-cel in the TRANSFORM trial, with a very short time between discontinuation of SOC and crossover to liso-cel, effectively meaning that the OS curves for both liso-cel and SOC in TRANSFORM are reflective of patients who have received liso-cel. Considering this, and in order to align with the approach taken for EFS, the use of independent survival models was also considered to represent the most appropriate approach for modelling OS for liso-cel and SOC, to ensure consistency between endpoints.

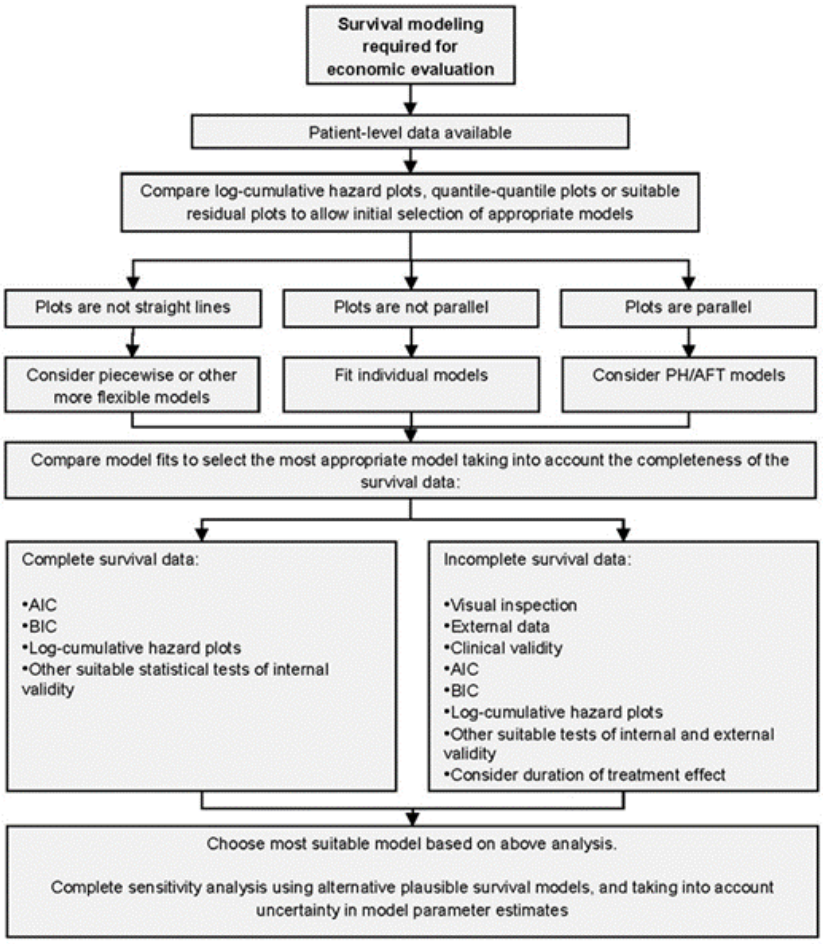
The use of individual fitted parametric models for both the intervention and comparator arms is aligned with the committee's preferred assumptions as part of TA895.

An SMR of 1.09, derived from the publication by Maurer *et al.* (2014), was used in the base case to adjust for excess mortality; this is applied to all patients considered in the model to be cured from the point of entry into the model.[129] This approach was validated with UK clinical experts and was in line with previous appraisals of CAR T-cell therapies, including the 3L+ DLBCL appraisals and TA895.[5, 133]

Methodology for curve selection

The choice of distribution for the base case for all EFS, OS and TTNT, curves followed algorithm shown in Figure 27 and the recommendations provided in NICE DSU TSD14[143]and TSD21.[140]

Figure 27: Algorithm for curve selection in TSD 14



Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TSD: Technical Support Document.
Source: NICE DSU TSD 14.[143]

The choice of distribution for the base case for all EFS, OS and TTNT curves was therefore informed considering:

- **Graphical assessment of fit:** the visual inspection can evaluate how well a parametric survival model fits with the observed Kaplan–Meier curves. The parametric survival model that most closely follows the Kaplan–Meier curve could be considered the best fit
- **Clinical plausibility of short and long-term extrapolations:** Feedback was obtained from two UK NHS Consultant Haematologists through pre-read questionnaire and from four UK NHS Consultant Haematologists through subsequent discussions via a virtual advisory board.[45] Consideration was given to both the clinical plausibility of the long-term extrapolations and the estimated cure fraction as well as the clinically plausibility of the extrapolations for non-cured patients over the short-term.
    - In the pre-read questionnaire, clinicians were asked to provide lower plausible limits, upper plausible limits and a most likely estimate for a cure fraction for EFS and OS for patients receiving liso-cel and SOC.[45] The lower and upper plausible limits are the values beyond which clinical experts believed it is extremely unlikely

for the true value to lie. Clinical experts were provided with the relevant baseline characteristics and the survival data from the final DCO (October 2023) of TRANSFORM as context to inform their estimates.

- **AIC/BIC tests:** the AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the selected model
- **Assessment of hazard functions**: comparison of the goodness of fit of modelled hazards to the (smoothed) hazards plot observed in the study to ensure the modelled hazard functions are in line with the observed data

B.3.3.3 EFS

Liso-cel

Visual inspection of fit

The extrapolations of EFS per IRC using individual patient data (IPD) from the TRANSFORM trial for each model up to 5 years are presented in Figure 28. Visual inspection shows that all extrapolations had good visual fit to the KM curve from TRANSFORM and there is a low degree of variation in survival estimates across the various models.

Clinical plausibility of long-term extrapolations for the combined cured and non-cured population

The extrapolations of EFS per IRC using IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure 29. A summary of the long-term projections of EFS for each extrapolation for cured and non-cured patients are presented in Table 36.

All extrapolations generated similar estimates of long-term survival (range: 40.5 – 46.3% at 15 years), reflecting the relatively low uncertainty associated with the choice of the EFS curve. UK clinical experts agreed all curves generated clinically plausible estimates of long-term survival for the combined cured and non-cured population.[45]

The choice of curve for the base-case was therefore based on consideration of the plausibility of the extrapolations of non-cured patients, alignment with the cure fraction predictions from clinicians and statistical fit to the observed KM data from TRANSFORM. The hazard profiles of the extrapolations were also compared to the observed hazard profiles from TRANSFORM to ensure the modelled hazard functions are in line with the observed data.

Plausibility of the extrapolations for non-cured patients and predicted cure fractions

Extrapolations of EFS per IRC using the IPD from the TRANSFORM trial for non-cured patients only is presented in Figure 30. The predicted cure fractions and projections of EFS for non-cured patients only for each extrapolation are presented in Table 36. Clinician estimates of predicted cure fractions for liso-cel gathered through pre-read questionnaires and discussions have also been presented in Table 36.

In TA895, clinical experts noted that patients who relapse would do so within 2 years.[5] Therefore, it was assumed any curves that estimated EFS to be higher than ~10% after 2 years were

considered to be clinically implausible.[5] Both the generalised gamma and Gompertz curves estimated EFS for non-cured patients to be greater than 10% at Year 2. In addition, the generalised gamma also estimated a cure fraction of 38.8%, which fell below the range of most likely values for a cure fraction elicited from the clinical experts ([redacted]%; range: [redacted]%–[redacted]%). The generalised gamma and Gompertz were therefore excluded from consideration as clinically implausible.

Plausibility of the hazard functions

A comparison of the smoothed hazard functions for the extrapolations and the observed KM data from TRANSFORM is presented in Figure 31. The figure demonstrates both the Gompertz and exponential distributions have hazard functions that do not align closely with the observed data from TRANSFORM, as they have decreasing hazards between 0-3 months whereas the trial data shows an increasing hazard during this timeframe. The exponential distribution was therefore also excluded given the poor fit to the observed hazards from TRANSFORM. The remaining distributions all have hazard functions broadly in line with the observed data and were considered further.

Selection of base case curve

AIC/BIC values for each extrapolation are presented in Table 35. Out of the remaining curves, the log-normal curve was selected for the base case as it was the best fitting model according to AIC ([redacted]; rank: 2) and BIC ([redacted]; rank 1) (once the Generalised Gamma was excluded). In addition, the log-normal had good visual fit to both the observed survival data and observed hazard function and estimated a cure fraction that was within [redacted] of the most likely estimate for a cure fraction provided by the clinical experts. The log-logistic curve also predicted a cure fraction that was within [redacted] of the most likely estimate for a cure fraction provided by the clinical experts but was not considered for the base-case as it has slightly worse statistical fit compared to the log-normal. The log-logistic curve was considered as an alternative scenario and results using this curve are presented in Section B.3.11.3.

Figure 28: Short-term extrapolations of EFS for liso-cel for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier.

Figure 29: Long-term extrapolations of EFS for liso-cel for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier.

Figure 30: Extrapolation of EFS for liso-cel for non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier.

Figure 31: Comparison of smoothed hazard functions between extrapolations and observed data for liso-cel EFS

Abbreviations: EFS: event-free survival.

Table 35: AIC and BIC statistics, EFS for liso-cel

Curve	Statistical fit			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	5	[redacted]	3
Weibull	[redacted]	6	[redacted]	5
Log-normal	[redacted]	2	[redacted]	1
Log-logistic	[redacted]	3	[redacted]	2
Gompertz	[redacted]	7	[redacted]	6
Generalised gamma	[redacted]	1	[redacted]	2
Gamma	[redacted]	4	[redacted]	4

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 36: Clinician and model estimates of EFS for liso-cel

Category	Curve	Cure fraction	EFS % for cured and non-cured patients					EFS % for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
Average clinician estimates (min, max)	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
TRANSFORM Data	TRANSFORM EFS KM	[redacted]	[redacted]	[redacted]								
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EFS: event-free survival; KM: Kaplan-Meier; NA: not applicable.

SOC

Visual inspection of fit

The extrapolations of EFS per IRC using the IPD from the TRANSFORM trial for each model up to Year 5 are presented in Figure 32. Visual inspection shows that all extrapolations had similar visual fit to the KM curve from TRANSFORM. The Weibull in particular had poor visual fit, appearing to underestimate EFS compared with the KM from TRANSFORM from ~Month 6 to the end of the observed data at Year 3.

Clinical plausibility of long-term extrapolations for the combined cured and non-cured population

The extrapolations of EFS per IRC using the IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure 33. A summary of the long-term projections of EFS for each extrapolation for cured and non-cured patients are presented in Table 38.

Similar to liso-cel, all extrapolations generated similar estimates of long-term survival (range: 17.4% – 19.1% at 15 years), reflecting the relatively low uncertainty associated with the choice of the EFS curve. Based on the feedback received during the advisory board, clinical experts agreed all the presented curves generated clinically plausible estimates of long-term EFS.[45]

Therefore, per the approach taken for liso-cel, the choice of curve for the base-case primarily considered the plausibility of the extrapolations of non-cured patients, alignment with the cure fraction predictions from clinicians, the hazard profile between liso-cel and SOC and statistical fit to the observed KM data from TRANSFORM. The hazard profiles were also compared to the observed hazard profiles from TRANSFORM to ensure the modelled hazard functions are in line with the observed data.

Plausibility of the extrapolations for non-cured patients and predicted cure fractions

Extrapolations of EFS per IRC using the IPD from the TRANSFORM trial for non-cured patients only is presented in Figure 34. The predicted cure fractions and projections of EFS for non-cured patients only for each extrapolation are presented in Table 38. Clinician estimates of predicted cure fractions for liso-cel gathered through pre-read questionnaires and discussions have also been presented in Table 38.

In line with the approach taken for curve selection for EFS for liso-cel, any curves that estimated EFS to be higher than ~10% at Year 2 were considered clinically implausible. For SOC, none of the curves predicted EFS higher than 10% at Year 2 and all the curves also generated estimated cure fractions that fell within the clinical experts range of most likely values. This reflects the relatively low uncertainty associated with EFS extrapolation.

Plausibility of the hazard functions

The next consideration was the underlying hazard functions of the extrapolations. A comparison of the smoothed hazard functions for the extrapolations and the observed KM data from TRANSFORM is presented in Figure 35. Similar to EFS for liso-cel, Figure 35 demonstrates both the Gompertz and exponential distributions have hazard functions that do not align closely with the observed data from TRANSFORM, as they have decreasing hazards between 0-3 months whereas the trial data shows a sharp increasing hazard during this timeframe. These

extrapolations were therefore not considered for the base-case. The Weibull and gamma distributions also do not fully capture the increasing hazard over the first 0-3 months observed from the trial data and overestimate the hazard during the middle part of the curve (Months 6 – 18). However, the hazard functions for these curves were not considered substantially different to be excluded based on the hazard function alone and therefore were considered further.

Selection of base case curve

As the remaining curves could not be excluded on the basis of clinical plausibility or consideration of the hazard profiles, selection of the base case curve was primarily based on alignment with liso-cel and consideration of statistical fit. AIC/BIC values for each extrapolation are presented in Table 37. NICE TSD 14 recommends fitting parametric models of the same type to both treatment arms in the absence of substantial justification that this would not be appropriate.[119] Given clinical experts in the advisory board meeting agreed the survival function for non-cured patients would be similar in the liso-cel and SOC arms, the approach to select the same type of extrapolation as liso-cel was considered the most appropriate.[45] The log-normal curve was therefore selected for the base case. This curve also had good statistical fit to the observed KM data and was the second-best fitting model according to AIC ([redacted]; rank: 2) and BIC ([redacted]; rank: 2). The generalised gamma was also considered a plausible curve choice as it was the best fitting model according to AIC ([redacted]; rank 1) and BIC ([redacted]; rank 1) and had a hazard profile that closely aligned with the observed hazards from TRANSFORM. A scenario analysis was therefore conducted using the generalised gamma curve (see Section B.3.11.3).

Figure 32: Short-term extrapolations of EFS for SOC for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care.

Figure 33: Long-term extrapolations of EFS for SOC for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care.

Figure 34: Extrapolation of EFS for SOC for non-cured patients using IPD from TRANSFORM

Abbreviations: EFS: event-free survival; IPD: individual patient data; SOC: standard of care.

Figure 35: Comparison of smoothed hazard functions between extrapolations and observed data for EFS for SOC

Abbreviations: EFS: event-free survival; IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care.

Table 37: AIC and BIC statistics, EFS for SOC

Curve	Statistical fit			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	5	[redacted]	5
Weibull	[redacted]	7	[redacted]	7
Log-normal	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	3	[redacted]	3
Gompertz	[redacted]	4	[redacted]	4
Generalised gamma	[redacted]	1	[redacted]	1
Gamma	[redacted]	6	[redacted]	6

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 38: Clinician and model estimates of EFS for SOC

Category	Curve	Cure fraction	EFS % for cured and non-cured patients					EFS % for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
Average clinician estimates	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
TRANSFORM	TRANSFORM EFS KM	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EFS: event-free survival; KM: Kaplan-Meier.

B.3.3.4 OS

Liso-cel

Visual inspection of fit

The extrapolations of OS using the IPD from the TRANSFORM trial for each model up to Year 5 are presented in Figure 36. Similar to EFS, visual inspection indicates all extrapolations had generally good visual fit to the KM curve from TRANSFORM, with the exception of the exponential curve which appears to underestimate survival between Year 0 – 1 and overestimate survival between Years 1 – 4 when compared to the KM from TRANSFORM.

Clinical plausibility of long-term extrapolations for the combined cured and non-cured population

The extrapolations of OS using the IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure 37. A summary of the long-term projections of OS for each extrapolation for the cured and non-cured patients are presented in Table 40.

All extrapolations generated similar estimates of long-term survival (range: 44.8% – 50.9% at 15 years), reflecting the relatively low uncertainty associated with the choice of the OS curve. UK clinical experts agreed all curves generated clinically plausible estimates of long-term survival for the combined cured and non-cured population.[45]

The choice of curve for the base-case was therefore based on consideration of the plausibility of the extrapolations of non-cured patients, alignment with the cure fraction predictions from clinicians and statistical fit to the observed KM data from TRANSFORM. The hazard profiles of the extrapolations were also compared to the observed hazard profiles from TRANSFORM to ensure the modelled hazard functions are in line with the observed data.

Plausibility of the extrapolations for non-cured patients and predicted cure fractions

Extrapolations of OS using the IPD from the TRANSFORM trial for non-cured patients only are presented in Figure 38. The predicted cure fractions and projections of EFS for non-cured patients only for each extrapolation are presented in Table 40. Clinician estimates of predicted cure fractions for liso-cel gathered through pre-read questionnaires and discussions have also been presented in Table 40.

In line with the approach taken for EFS but accounting for the additional follow-up needed to observe OS events, it was assumed the majority of non-cured patients would die within 4 years and less than ~10% of patients would be alive at approximately 4 years. With a prediction that 15.6% of non-cured patients would be alive after 4 years, the exponential distribution was considered clinically implausible.

Plausibility of the hazard functions

A comparison of the smoothed hazard functions for the OS extrapolations and the observed KM data from TRANSFORM is presented in Figure 39. The figure also supports excluding the exponential distribution. By definition, the exponential curve assumes a constant hazard of death for non-cured patients across the model time horizon and, as shown in Figure 39 below, this constant hazard fails to accurately capture the changing hazard profile observed in

TRANSFORM. Given this, and the poor visual fit to the observed KM data from TRANSFORM, the exponential curve was excluded from further consideration.

Similar to the exponential, the Gompertz curve also shows poor visual fit to the observed hazard profile from TRANSFORM and underestimates the hazard across the first 16 months of the observed data. The Gompertz curve was therefore also excluded given the poor fit to the observed hazards from TRANSFORM. The remaining distributions all have hazard functions in line with the observed data and were considered further.

Selection of base case curve

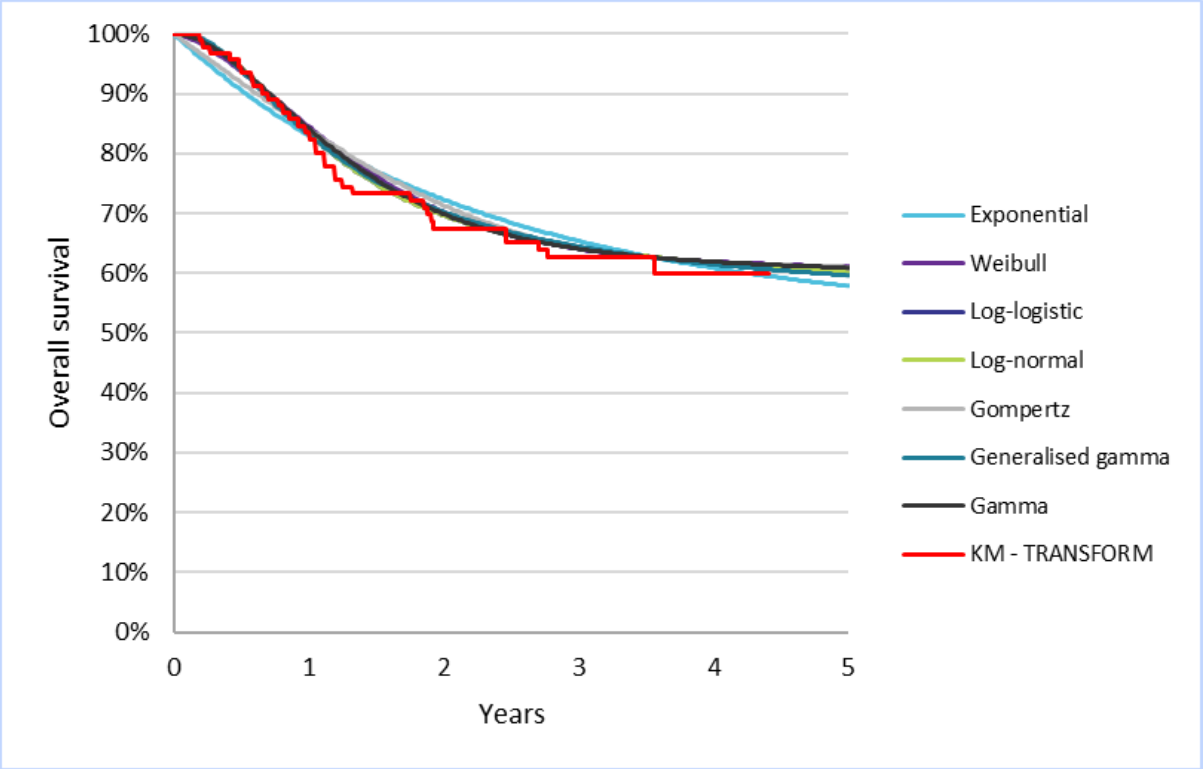
Once the exponential and Gompertz were excluded, of the remaining curves, the Weibull and Gamma were not considered for the base case because they were considered overly pessimistic, predicting a low percentage of non-cured patients would be alive at Year 4 (1.0% and 1.7%, respectively) and had poorer visual fit to the observed hazard profile compared to the log-logistic, log-normal and generalised gamma curves.

The log-logistic, log-normal and generalised gamma curves were all considered plausible and estimated a similar percentage of non-cured patients would be alive at Year 4 (7.1%, 7.6% and 8.5%, respectively). The log-normal curve was selected for the base case as it was the best fitting model according to AIC (355.1; rank: 1) and BIC (362.6; rank 1) and predicted a survival percentage in the middle of the remaining curves and therefore considered the most plausible curve. In addition, the log-normal provided good visual fit to the observed data and generated clinically plausible estimates of long-term survival when considering the combined cured and non-cured patients and the non-cured patients only.[45] Of note, the cure fraction for the log-normal curve (60.8%) was slightly outside the range for the most likely value provided by clinicians ([redacted]). However, this range was based on estimates provided by just two clinicians, with one providing an estimate of [redacted] and the other [redacted] so the estimate from the log-normal curve could be considered plausible as it was directly aligned with one of the clinician's estimates.

Alternative extrapolations have been provided using the Weibull (a more optimistic curve) and the generalised gamma (a more pessimistic curve) to assess the impact on the results. Results using these alternative curves are presented in Section B.3.11.3.

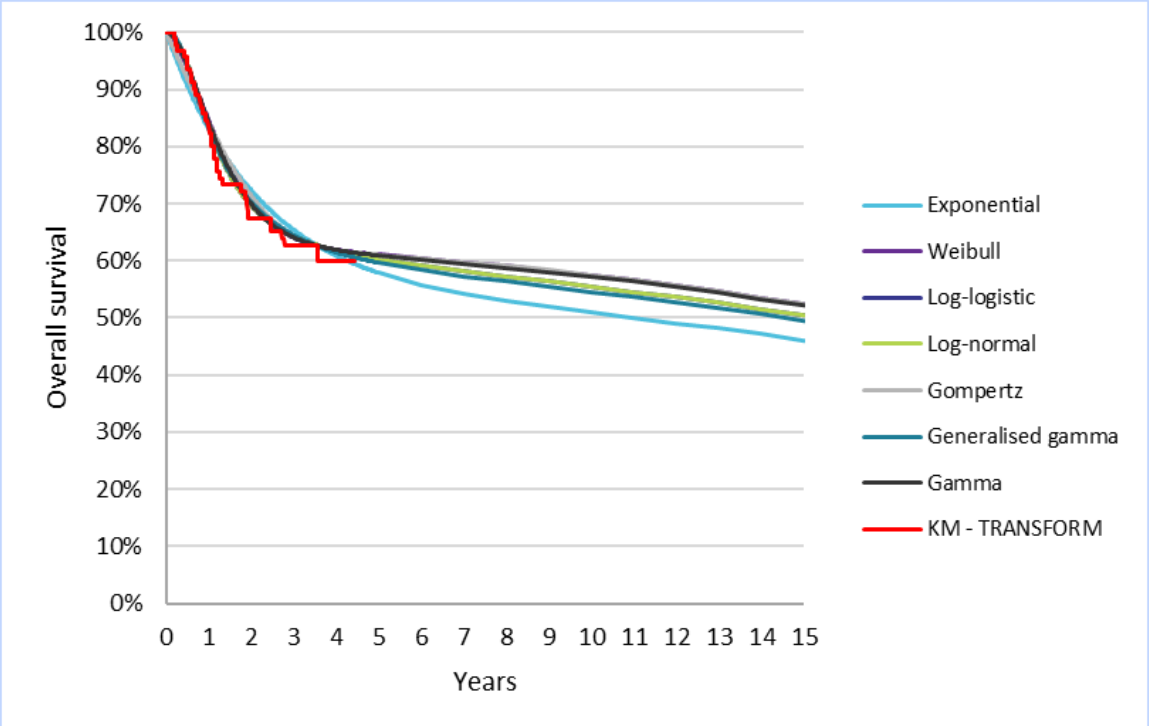
It should be noted, as discussed in Section B.2.12.2 and B.3.2.4, it is expected that using the TRANSFORM trial to model the outcomes in the liso-cel arm underestimates the overall survival, relative to UK clinical practice. This is because in UK clinical practice, patients who receive liso-cel at 2L would now receive 3L+ bispecifics if they require a subsequent treatment, which were not available at the time of the TRANSFORM trial. As bispecific antibodies have been shown to be more effective than chemotherapy (the primary subsequent treatment received in the liso-cel arm of TRANSFORM), the economic analysis presented is considered a conservative approach.[45]

Figure 36: Short-term extrapolations of OS for liso-cel for cured and non-cured patients using IPD from TRANSFORM



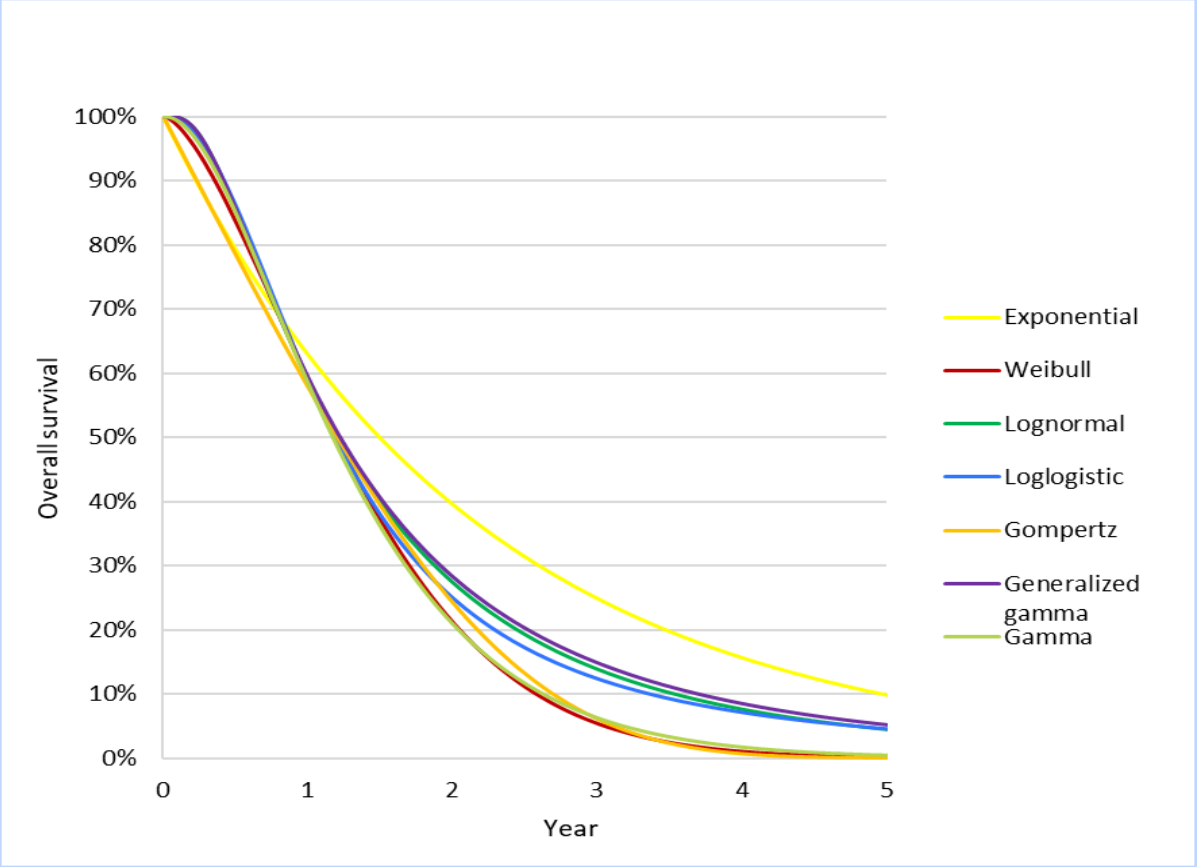
Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Figure 37: Long-term extrapolations of OS for liso-cel for cured and non-cured patients using IPD from TRANSFORM



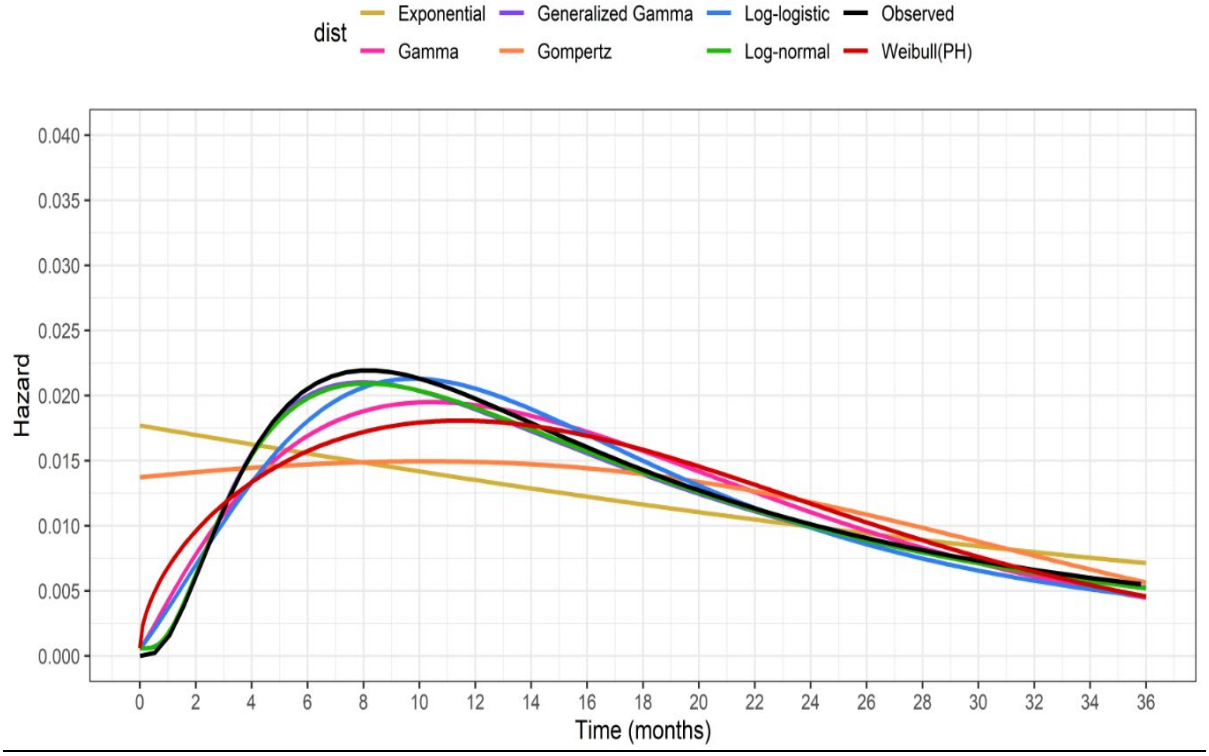
Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Figure 38: Extrapolation of OS for non-cured patients using IPD from TRANSFORM



Abbreviations: IPD: individual patient data; KM: Kaplan-Meier: OS: overall survival.

Figure 39: Comparison of smoothed hazard functions between extrapolations and observed data for liso-cel OS



Abbreviations: OS: overall survival.

Table 39: AIC and BIC statistics, OS for liso-cel

Curve	Statistical fit			
	AIC	Rank	BIC	Rank
Exponential	359.9	5	364.9	5
Weibull	357.1	4	364.6	4
Log-normal	355.1	1	362.6	1
Log-logistic	355.3	2	362.9	2
Gompertz	360.4	6	368.0	6
Generalised gamma	357.1	4	368.0	6
Gamma	356.0	3	363.5	3

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Table 40: Clinician and model estimates of OS for liso-cel

Category	Curve	Cure fraction	Median OS (years)	OS% for cured and non-cured patients					OS% for non-cured patients				
				1	2	5	10	15	1	2	3	4	5
Average clinician estimates	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-	-
TRANSFORM	TRANSFORM OS KM	NA	NE	83.5	67.5	-	-	-	-	-	-	-	-
Extrapolations	Exponential	55.8	10.0	82.8	72.0	57.5	50.2	44.8	62.4	39.3	24.8	15.6	9.8
	Weibull	63.4	15.0	84.1	69.9	60.7	56.6	50.9	58.3	20.9	5.3	1.0	0.2
	Log-normal	60.3	13.0	82.8	70.0	59.4	54.0	48.5	58.3	27.1	13.8	7.6	4.5
	Log-logistic	60.8	14.0	83.0	69.4	59.9	54.7	49.0	58.2	24.7	12.3	7.1	4.6
	Gompertz	63.4	15.0	83.7	71.1	60.7	56.6	50.9	57.2	23.9	6.0	0.7	0.0
	Generalised gamma	59.9	13.0	82.8	70.0	59.3	53.7	48.2	58.6	28.0	14.8	8.5	5.2
	Gamma	63.1	15.0	83.8	69.6	60.5	56.4	50.7	57.7	20.6	6.2	1.7	0.4

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; NE: not estimable; OS: overall survival.

SOC

Visual inspection of fit

The extrapolations of OS using the IPD from the TRANSFORM trial for each model up to Year 5 are presented in Figure 40. For SOC OS, visual inspection indicates all extrapolations had good visual fit to the KM curve from TRANSFORM.

Clinical plausibility of long-term extrapolations for the combined cured and non-cured population

The extrapolations of OS per IRC using the IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure 41. A summary of the long-term projections of OS for each extrapolation for the cured and non-cured patients are presented in Table 42. Predicted cure fractions from the extrapolations and clinician estimates of cure fractions for SOC OS gathered through pre-read questionnaires and discussions have also been presented in Table 42.

All extrapolations generated similar estimates of long-term survival (range: 40.7% – 43.8% at 15 years). However, clinical expert feedback indicated that all the extrapolations appeared to overestimate survival and none of the presented extrapolations aligned with clinical expectations of long-term survival for patients receiving 2L SOC in clinical practice.[45] In addition, all the extrapolations estimated cure fractions that fell above the upper range of the most likely value of a cure fraction elicited from the clinical experts. During the advisory board, clinical experts agreed a 50% cure rate for SOC is reflective of the late relapsed population and is therefore not applicable to this harder to treat, primary refractory/early relapse population.[45]

The survival estimates for SOC OS derived from TRANSFORM data may be higher than expected in UK clinical practice due to the design of the TRANSFORM trial.[41] The proportion of patients requiring a subsequent treatment (i.e. who experienced an event) who received 3L+ CAR-T in TRANSFORM (93.85%; [redacted] is expected to be higher than UK clinical practice, based on estimates from UK clinicians (66.25%). Further, as discussed in Section B.2.12.2, in TRANSFORM all patients were apheresed before randomisation, meaning the patients who did not respond to SOC received CAR-T therapy within a median of [redacted].[41, 115] This does not align with UK clinical practice, where patients would undergo apheresis and CAR-T manufacture only after progression on 2L treatment. This would delay CAR-T therapy receipt and therefore reduce the proportion of responders as patients disease worsens during this delay. Furthermore, in TRANSFORM patients receiving SOC were apheresed at 2L whereas in UK clinical practice, this would occur after progression on 2L treatment (i.e. 3L+). It is therefore likely the leukapheresed cells collected in TRANSFORM were healthier compared to those that would be collected for patients receiving 3L+ CAR-T cell therapy in UK clinical practice, which may also contribute to the improved survival outcomes observed in the SOC arm of TRANSFORM.

Plausibility of the hazard functions

For completeness, a comparison of the smoothed hazard functions for the OS extrapolations and the observed KM data from TRANSFORM is presented in Figure 39. The figure demonstrates both the Gompertz and exponential distributions have poor visual fit to the observed data from TRANSFORM but all other extrapolations have hazard functions broadly in line with the observed data.

Selection of base case curve

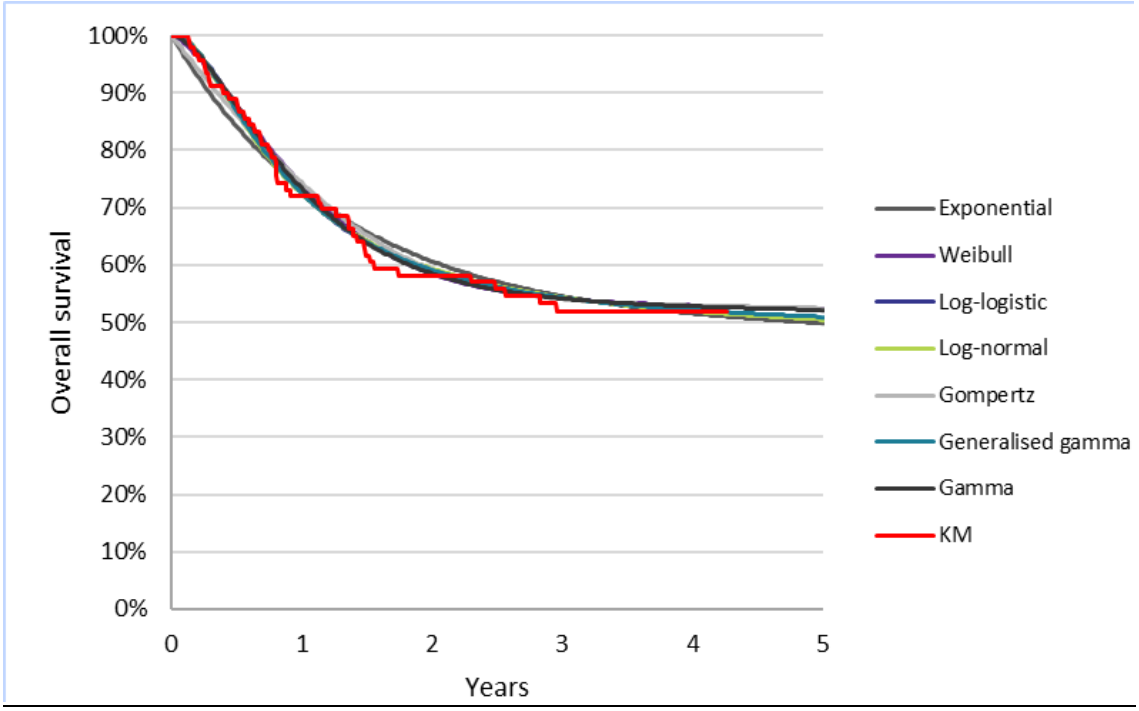
AIC/BIC values for each extrapolation are presented in Table 35. Predicted cure fractions from the extrapolations are presented in Table 42.

Given all extrapolations overestimated survival, the curve choice for SOC OS was primarily based on statistical fit. The log-normal curve was therefore selected for the base case as it was the best fitting model according to AIC (406.9; rank: 1) and BIC (414.5; rank 1). The log-normal was also considered the most clinically plausible curve as it estimated the joint lowest cure fraction (50.7%) and unlike the exponential (which also estimated a cure fraction of 50.7%), the log-normal had good visual fit to the observed hazard profile from TRANSFORM.

Despite choosing the curve with the lowest cure fraction, this is still considered a conservative approach as this curve likely overestimates the survival for patients receiving SOC based on clinical expert feedback and therefore biases the comparison between liso-cel and SOC in favour of SOC.

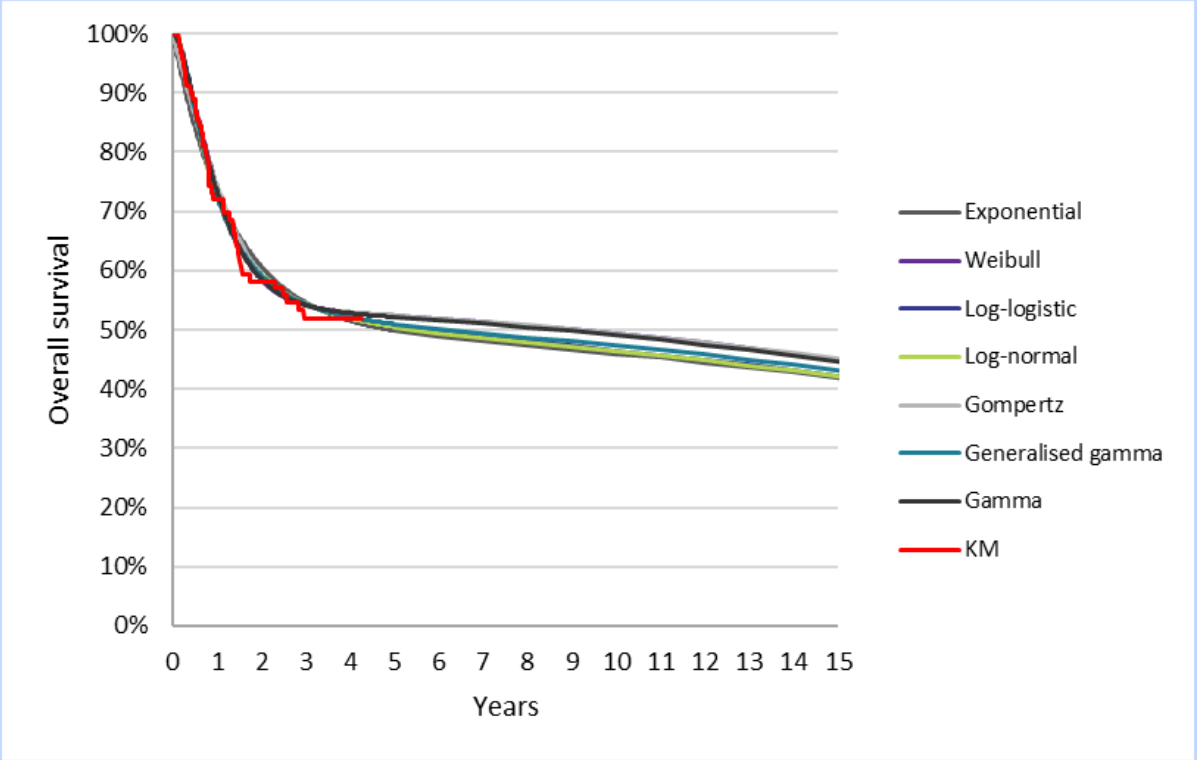
Given the clear need to generate more plausible estimates of overall survival for SOC, a scenario analysis has been explored that uses data from the CORAL study to reweight the SOC OS curve and bring the estimates of survival for SOC down into a more plausible range. The CORAL trial investigated outcomes for SOC in this patient population prior to the availability of 3L+ CAR-T cell therapies, so may more accurately reflect the OS outcomes for patients receiving SOC who do not go onto receive 3L+ CAR-T cell therapy with axi-cel.[144] Details of the methodology for incorporation of the CORAL study and results from this scenario analysis are provided in Section B.3.11.3.

Figure 40: Short-term extrapolations of OS for SOC for cured and non-cured patients using IPD from TRANSFORM



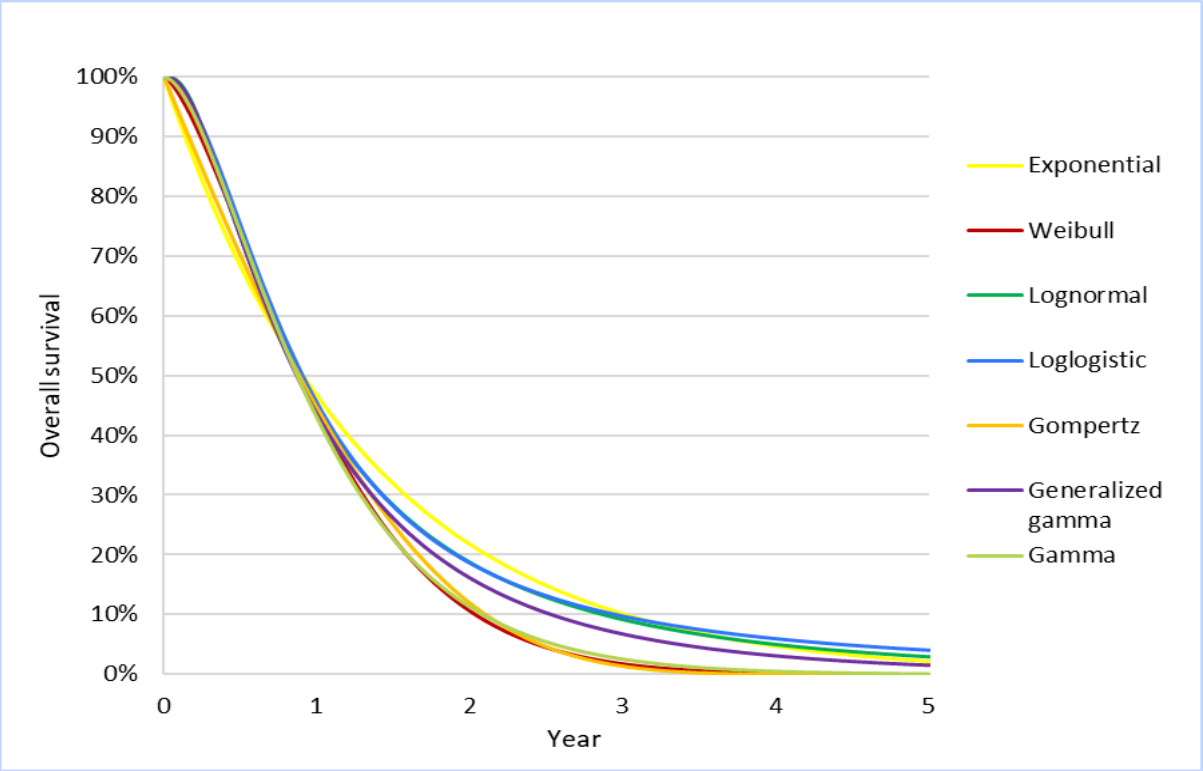
Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival; SOC: standard of care.

Figure 41: Long-term extrapolations of OS for SOC for cured and non-cured patients using IPD from TRANSFORM



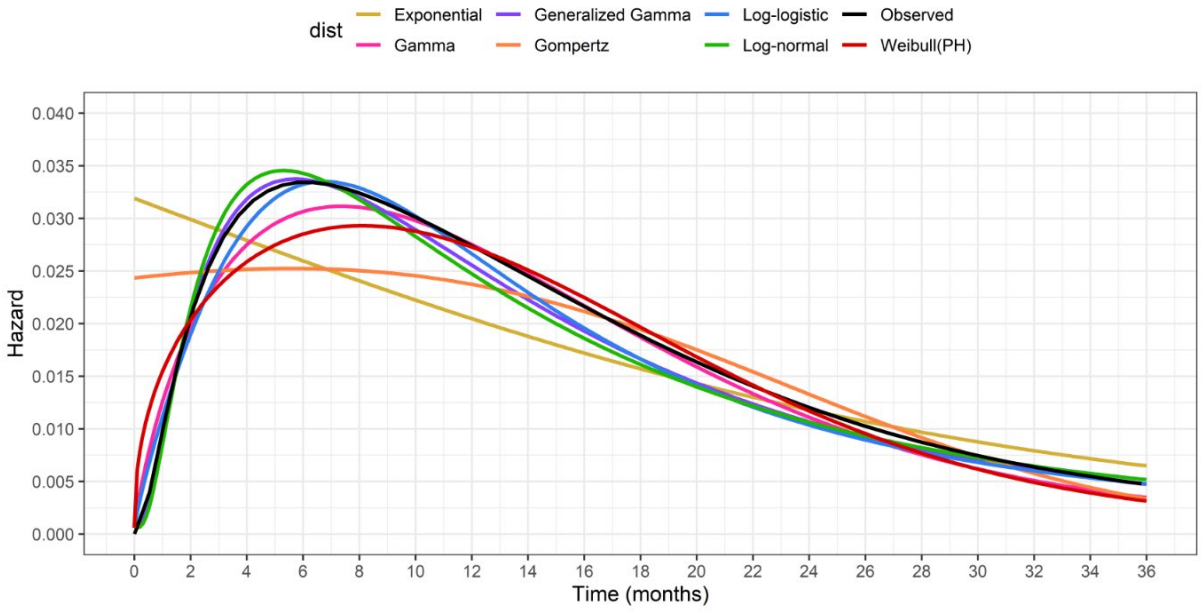
Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival; SOC: standard of care.

Figure 42: Extrapolation of OS for non-cured patients using IPD from TRANSFORM



Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival; SOC: standard of care.

Figure 43: Comparison of smoothed hazard functions between extrapolations and observed data for SOC OS



Abbreviations: OS: overall survival; SOC: standard of care.

Table 41: AIC and BIC statistics, OS for SOC

Curve	Statistical fit

	AIC	Rank	BIC	Rank
Exponential	411.2	6	416.2	5
Weibull	408.2	3	415.8	4
Log-normal	406.9	1	414.5	1
Log-logistic	407.4	2	414.9	2
Gompertz	411.1	5	418.7	6
Generalised gamma	408.9	4	418.9	7
Gamma	407.4	2	415.0	3

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; SOC: standard of care.

Table 42: Clinician and model estimates of OS for SOC

Category	Curve	Cure fraction	Median OS (years)	OS% for cured and non-cured patients					OS% for non-cured patients				
				1	2	5	10	15	1	2	3	4	5
Average clinician estimates	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-	-
TRANSFORM	TRANSFORM OS KM	NA	NE	72.0	58.2	-	-	-	-	-	-	-	-
Extrapolations	Exponential	50.7	4.7	72.9	60.4	49.5	45.3	40.7	46.1	21.6	10.1	4.7	2.2
	Weibull	54.4	8.0	73.5	58.3	52.1	48.6	43.7	43.0	10.4	1.8	0.2	0.0
	Log-normal	51.0	5.0	72.0	59.1	50.2	45.7	41.0	44.0	18.6	9.2	5.0	3.0
	Log-logistic	50.7	5.0	72.2	58.9	50.4	45.8	41.0	44.6	18.4	9.6	5.9	3.9
	Gompertz	54.5	8.0	73.9	58.9	52.1	48.7	43.8	43.9	11.7	1.4	0.0	0.0
	Generalised gamma	52.2	5.0	72.1	58.9	50.6	46.6	41.9	42.8	16.0	6.7	3.1	1.6
	Gamma	54.1	7.0	72.9	58.3	51.8	48.3	43.5	42.1	11.1	2.5	0.5	0.1

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; NE: not estimable; OS: overall survival.

B.3.3.5 Time to next treatment

As discussed in Section B.3.3.2, proportional hazards assessments were not available for TTNT at the time of submission. However, given the similarity between the EFS and TTNT results, it is likely the proportional hazards assumption would also not hold for TTNT and therefore independent survival models for TTNT for liso-cel and SOC were fitted.

For TTNT, it was assumed any patients who do not experience a TTNT event by Year 5 are assumed to be cured and therefore any subsequent treatments they receive would not be for their original early relapsed/primary refractory LBCL. This is also in line with the approach taken in TA895.[5]

Liso-cel

Visual inspection of fit

The extrapolations of TTNT using the IPD from the TRANSFORM trial for each model up to Year 5 are presented in Figure 44. Visual inspection indicates all extrapolations provided a generally good visual fit to the KM curve from TRANSFORM, with the exception of the exponential curve which appears to underestimate the percentage of patients on 2L treatment from the start of the KM curve to ~Month 6 and then overestimate the percentage of patients on 2L treatment between Month 6 and Year 2, compared to the KM from TRANSFORM.

Clinical plausibility of long-term extrapolations for the combined cured and non-cured population

The extrapolations of TTNT using the IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure 45. A summary of the long-term projections of TTNT for each extrapolation for cured and non-cured patients are presented in Table 44.

All extrapolations generated similar estimates of long-term survival (range: 45.6% – 49.0% at 15 years), reflecting the relatively low uncertainty associated with the choice of the TTNT curve. TTNT was not validated during the advisory board but the estimates are broadly in line with the estimates for EFS, which were considered plausible.

The choice of curve for the base-case was therefore based on consideration of the plausibility of the extrapolations of non-cured patients, alignment with the cure fraction predictions from clinicians and statistical fit to the observed KM data from TRANSFORM.

Plausibility of the extrapolations for non-cured patients and predicted cure fractions

Extrapolations of TTNT using the IPD from the TRANSFORM trial for non-cured patients only is presented in Figure 46. The predicted cure fractions and projections of TTNT for non-cured patients for each extrapolation are presented in Table 44. Clinician estimates of predicted cure fractions for EFS for liso-cel gathered through pre-read questionnaires and discussions have also been presented in Table 44.

In line with the approach taken for curve selection for EFS, given the expected similarity between the EFS and TTNT endpoints, it was assumed any curves that estimated TTNT to be higher than ~10% after 2 years for non-cured patients were considered to be clinically implausible as after two years, the majority of non-cured patients would be expected to have received a subsequent

treatment or died.[5] Both the exponential and generalised gamma estimated TTNT for non-cured patients to be greater than 10% at Year 2. The exponential and generalised gamma were therefore excluded from consideration due to their clinical implausibility. Additionally, the poor visual fit to the KM curve for the exponential curve further supported this exclusion.

Selection of base case curve

AIC/BIC values for each extrapolation are presented in Table 43. The log-normal curve was selected for the base case as it was the best fitting model according to AIC ([redacted]; rank 2) and BIC ([redacted]; rank 2), once the Generalised Gamma was excluded for clinical plausibility. In addition, the log-normal provided a good visual fit to the observed data, and estimated a cure fraction that was considered clinically plausible when compared to the clinician estimates for liso-cel EFS (which was assumed to be applicable to TTNT). The log-logistic curve also predicted a cure fraction that was considered clinically plausible but was not considered for the base-case as it has slightly worse statistical fit compared to the log-normal. The log-logistic curve has been considered as an alternative scenario and results using this curve are presented in Section B.3.11.3.

Figure 44: Short-term extrapolations of TTNT for liso-cel for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; TTNT: time to next treatment.

Figure 45: Long-term extrapolations of TTNT for liso-cel for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; TTNT: time to next treatment.

Figure 46: Extrapolation of TTNT for non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; TTNT: time to next treatment.

Table 43: Goodness-of-fit statistics for liso-cel for TTNT survival models

Survival model	Liso-cel			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	5	[redacted]	5
Log-normal	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	3	[redacted]	3
Gompertz	[redacted]	7	[redacted]	7
Generalised gamma	[redacted]	1	[redacted]	1
Gamma	[redacted]	4	[redacted]	4

Footnote: Bold indicates lowest AIC/BIC value and base-case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTNT: time to next treatment.

Table 44: Clinician and model estimates of TTNT for liso-cel

Category	Curve	Cure fraction	TTNT% for cured and non-cured patients					TTNT% for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
Average clinician estimates (for liso-cel EFS)	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
TRANSFORM	TRANSFORM TTNT KM	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; TTNT: time to next treatment.

SOC

Visual inspection of fit

The extrapolations of TTNT using the IPD from the TRANSFORM trial for each model up to Year 5 are presented in Figure. Visual inspection shows that all extrapolations had similar visual fit to the KM curve from TRANSFORM.

Clinical plausibility of long-term extrapolations

The extrapolations of TTNT using the IPD from the TRANSFORM trial for each model up to Year 15 are presented in Figure. Extrapolations of TTNT using the IPD from the TRANSFORM trial for non-cured patients only is presented in Figure. A summary of the long-term projections of TTNT for each extrapolation for cured and non-cured patients are presented in Table 46.

All extrapolations generated very similar estimates for the proportion of patients on 2L treatment (range: 23.2% – 23.3% at 15 years), and very similar cure fractions (range: 23.2% – 23.3%); this is likely driven by the very flat plateau observed in the KM data from TRANSFORM from Year 1 onwards, and means there is a low amount of uncertainty associated with the choice of TTNT curve. Furthermore, for SOC, none of the curves predicted TTNT higher than 10% at Year 2 and for non-cured patients, so there was no reason to exclude any of the curves for clinical plausibility in this regard.

Selection of base case curve

As curves could not be excluded on the basis of clinical plausibility, in line with the approach taken for EFS, selection of the base case curve for SOC TTNT was primarily based on alignment with liso-cel and also consideration of statistical fit. This was because NICE TSD 14 recommends fitting parametric models of the same type to both treatment arms in the absence of substantial justification that this would not be appropriate.[119]

The log-normal curve was therefore selected for the base case, to align with the TTNT curve selected for liso-cel. This log-normal provided a good statistical fit to the observed KM data (Table 45) and was the third-best fitting model according to AIC ([redacted]; rank: 3) and BIC ([redacted] rank: 3). The log-logistic was also considered a plausible curve choice as it was the joint best fitting model according to AIC ([redacted]; rank 2) and BIC ([redacted]; rank 1), and was therefore explored in a scenario analysis (see Section B.3.11.3).

Figure 47: Short-term extrapolations of TTNT for SOC for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care; TTNT: time to next treatment.

Figure 48: Long-term extrapolations of TTNT for SOC for cured and non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care; TTNT: time to next treatment.

Figure 49: Extrapolation of TTNT for SOC for non-cured patients using IPD from TRANSFORM

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; SOC: standard of care; TTNT: time to next treatment.

Table 45: Goodness-of-fit statistics for SOC for TTNT survival models

Survival model	SOC			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	6	[redacted]	5
Weibull	[redacted]	5	[redacted]	6
Log-normal	[redacted]	3	[redacted]	3
Log-logistic	[redacted]	2	[redacted]	1
Gompertz	[redacted]	7	[redacted]	7
Generalised gamma	[redacted]	1	[redacted]	2
Gamma	[redacted]	4	[redacted]	4

Footnote: Bold indicates lowest AIC/BIC value and base-case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; SOC: standard of care; TTNT: time to next treatment.

Table 46: Clinician and model estimates of TTNT for SOC

Category	Curve	Cure fraction, %	TTNT% for cured and non-cured patients					TTNT% for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
Average clinician estimates (for SOC EFS)	Lower plausible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
	Most likely value	[redacted]	-	-	-	-	-	-	-	-	-	-
	Upper possible limit	[redacted]	-	-	-	-	-	-	-	-	-	-
TRANSFORM	TRANSFORM TTNT KM	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; SOC: standard of care; TTNT: time to next treatment.

B.3.3.6 Summary of survival approaches

An overview of the chosen EFS, OS and TTNT extrapolations for liso-cel and SOC is presented below in Table 47.

In the model, all projected EFS curves are capped by the OS curves to ensure that the proportion of patients in the EFS health state remains equal to or less than the proportion in the OS health state at any given time over the model time horizon. In line with previous appraisals of CAR T-cell therapies, including the 3L+ DLBCL appraisals, an SMR of 1.09, derived from the publication by Maurer *et al.* (2014) was used in the base case to adjust for excess mortality in long-term survivors.[5, 129] UK clinical and health economic experts confirmed that this represented an appropriate approach.[45]

The model also includes additional constraints to ensure that the probability of survival in each cycle cannot exceed that of the SMR adjusted age- and sex-matched general population of the UK. This capping is not applied in the statistical output curves shown in the above figures but has been included in Figure 50 and Figure 51 below, which present the base-case projections of EFS and OS, respectively.

For TTNT, it was assumed any patients who do not experience a TTNT event by Year 5 are assumed to be cured and therefore do not receive a subsequent treatment, in line with the approach taken in TA895.[5] The base-case projections for TTNT up to Year 5 are presented in Figure.

Table 47: Summary of base case survival approaches

	Liso-cel	SOC
EFS	Log-normal	Log-normal
OS	Log-normal	Log-normal
TTNT	Log-normal	Log-normal

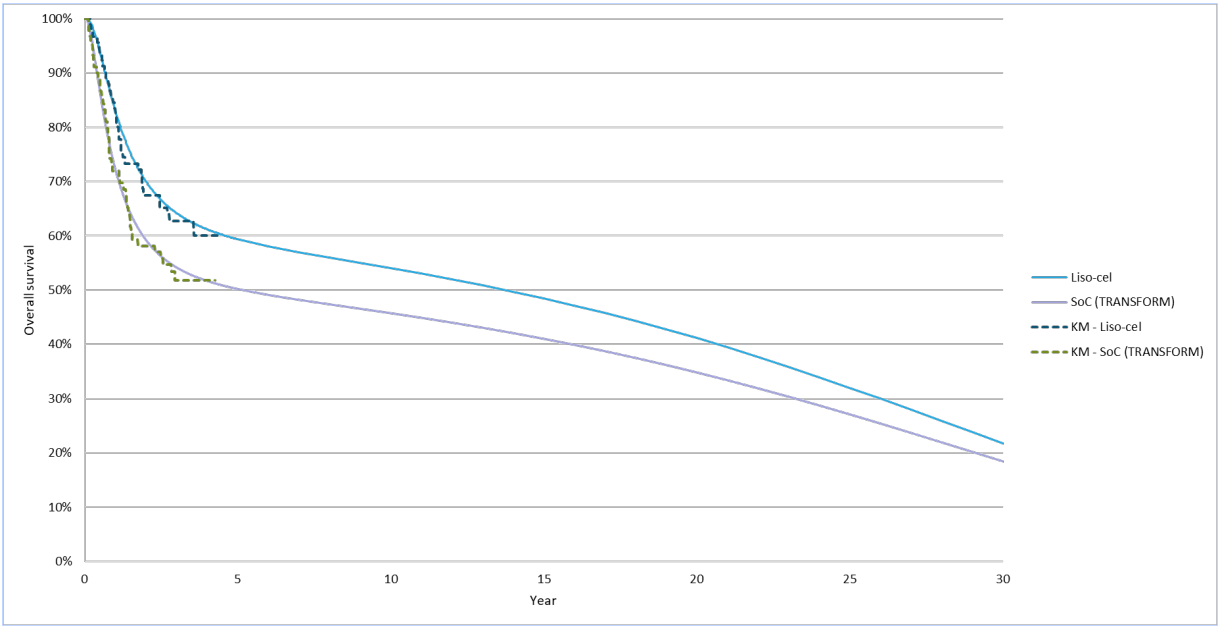
Abbreviations: EFS: event-free survival; OS: overall survival; TTNT: time to next treatment SOC: standard of care.

Figure 50: Modelled base-case extrapolations for EFS

[redacted]

EFS curves are capped by OS.
Abbreviations: EFS: event-free survival.

Figure 51: Modelled base-case extrapolations for OS



OS curves are capped by general population mortality.
Abbreviations: OS: overall survival.

Figure 52: Modelled base-case extrapolations for TTNT

Any patients who do not experience a TTNT event by Year 5 are assumed to be cured and therefore do not receive a subsequent treatment.
Abbreviations: 2L: second-line; KM: Kaplan-Meier; TTNT: time to next treatment; SOC: standard of care.

B.3.3.7 Adverse events

The model considers Grade ≥3 treatment-related AEs that occurred in at least 5% of patients in either the liso-cel or SOC arm of the TRANSFORM trial as well as AESIs for CAR-T therapies (i.e. CRS, neurotoxicity and hypogammaglobulinemia) of any grade.

Grade 1 and 2 non-AESIs were not considered in the model as these are unlikely to be associated with considerable health-related costs or changes in patient HRQoL, in line with the approach taken for TA895.[5] Given AESIs may be associated with significant resource use at any grade, AESIs were considered in the model regardless of grade and incidence.

Utility decrements were also included in the model and applied for all Grade ≥3 treatment-related AEs and for all Grade ≥3 AESIs.

The incidence of Grade ≥3 treatment-related AEs that occurred in at least 5% of patients as well as the incidence of AESIs for CAR-T therapies (CRS, neurotoxicity and hypogammaglobulinemia) of any grade from the TRANSFORM trial are presented in Table 48.

In the base-case economic analysis, the costs associated with the management of treatment-related AEs and AESIs (with the exception of the costs associated with treating hypogammaglobulinemia with IVIg) were assumed to be already captured within one-off CAR-T tariff cost (described in Section B.3.5.1). For SOC, the costs associated with the management of

treatment-related AEs and AESIs were calculated granularly, based on the incidences detailed in Table 48. The utility decrements associated with the Grade ≥3 AEs and AESIs are presented in Section B.1.1.1 and the costs associated with the management of AEs are presented in Section B.3.5. Where relevant, the costs and utility decrements of AEs were applied as a one-off in the first cycle of the model (i.e. when all patients are still alive).

Table 48: Summary of Grade ≥3 AEs occurring in ≥5% of patients considered in the economic model

AE	Liso-cel (n=92)	SOC (n=91)	Source
AESIs			TRANSFORM CSR (final DCO; October 2023)[41]
CRS (any grade)	48.9%	0.0%	
CRS (Grade ≥3)	1.1%	0.0%	
Neurotoxicity (any grade)	10.9%	[redacted]	
Neurotoxicity (Grade ≥3)	4.3%	[redacted]	
Hypogammaglobulinemia (any grade)	[redacted]	[redacted]	
Hypogammaglobulinemia (Grade ≥3)	[redacted]	[redacted]	
Non-AESIs (Grade ≥3 occurring in at least 5% of patients)			
Neutropenia	81.5%	51.6%	
Thrombocytopenia	50.0%	68.1%	
Anaemia	52.2%	56.0%	
Lymphopenia	26.1%	9.9%	
Febrile neutropenia	[redacted]	[redacted]	
Leukopenia	16.3%	13.2%	
Prolonged cytopenia	43.5%	3.3%	
Hypophosphatemia	[redacted]	[redacted]	
Infections	15.2%	20.9%	
Hypertension	[redacted]	[redacted]	

Abbreviations: AE: adverse event; CSR: case study report; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.3.4 *Measurement and valuation of health effects*

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

The base-case utilities were estimated based on the EQ-5D-5L data collected in the TRANSFORM trial (final DCO; October 2023).[41] Data were collected at the following timepoints:

- At randomisation (baseline): Day 1 (+3 days)
- During treatment period: Day Days 29 (±7 days), 64 (±6 days), 126 (±7 days)
- During post-treatment period: Month 6 (±10 days) and Months 9, 12, 18, 24 and 36 (±14 days), among subjects who have not received subsequent treatment

Utility index scores were generated using the preference-weights for UK reported by Dolan *et al.* (1997).[145] Therefore, the utility values presented in Section B.3.4.6 are representative of the population of interest in UK clinical practice.

B.3.4.2 Mapping

HRQoL data were collected in the TRANSFORM trial using the EQ-5D-5L.[41] In accordance with the NICE position statement on the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from TRANSFORM were mapped onto the 3L UK value set using the mapping function developed by Hernandez Alava *et al.* (2017) through the NICE Decision Support Unit (DSU) using the EEPRU dataset (Hernandez Alava *et al.* 2020).[146-148] The resulting utility values derived from the mapping are presented in Section B.3.4.6.

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

An SLR conducted to identify evidence on HRQoL, PROs and utilities in patients with early relapsed/primary refractory LBCL. No restrictions were applied to the transplant-eligibility of patients to broaden the evidence base. Full details of the SLRs conducted are presented in Appendix H.

The HRQoL SLR was originally conducted on 21st April 2020 with subsequent updates performed on 8th June 2020, 5th February 2021, 2nd May 2022, 1st March 2023 with the most recent update conducted on 1st February 2024.

Of the 92 publications reporting on 71 unique studies that met the SLR inclusion criteria, 28 unique studies (16 economic evaluations, six clinical trials, four HTA reports, one point-in-time survey and one utility study) reported data specific to 2L and 2L+ patients. Four studies, one vignette study and two HTA reports reported health-state utility values in study populations which included the UK. Details of these identified studies are summarised in Table 49 below.

Table 49: Summary of relevant studies reporting on health-state utility values

Study	Type of study	Patient Population	Treatment	Utility Instrument	Utility Values
Elsawy *et al.* (2022); ZUMA-7 trial[149]	Phase III, open-label RCT	Patients with R/R LBCL within 12 months of first-line immunochemotherapy and intended to proceed to HDCT-ASCT	Axi-cel vs. SOC (chemotherapy + HSCT)	EQ-5D-5L (visual analogue scale)	Not relevant
				EQ-5D-5L (health utility index)	*Baseline, mean (SD):* Axi-cel: 0.803 SOC: 0.799 *Mean change at last follow-up (SD):* Day 50: Axi-cel: -0.049 SOC: -0.003
Westin *et al.* (2023); ZUMA-7 trial[150]		Patients ≥ 65 years with 2L R/R LBCL including DLBCL not further defined and NOS, tFL, HGBCL		EQ-5D-5L (visual analog scale)	Not relevant
Wang *et al.* (2018)[151]	Utility study	DLBCL patients newly diagnosed 2004-15 who completed one or more EQ-5D-5L questionnaire	Second-line treatment (unspecified)	EQ-5D-5L value set (UK)	*Baseline, mean (SD):* 2L: 0.66 (SE: 0.025) *Second remission:* 0.81 (SE: 0.057)
				EQ-5D-5L crosswalk index value (mapping to EQ-5D-3L values)	*Baseline, mean (SD):* 2L: 0.53 (SE: 0.065) *Second remission:* 0.69 (SE: 0.081)
Orfanos *et al.* (2022)[152]	Phase II single-arm trial	2L and Heavily Pre-Treated Patients with R/R DLBCL	Naratuximab Emtasine + Rituximab	EQ-5D (unspecified)	*Baseline, mean (SD):* • Responders: 0.78 (NR) • Non-responders: 0.73 (NR) *End of therapy, mean (SD):* • Responders: 0.77 (NR) • Non-responders: 0.67 (NR)

Soare *et al.* (2023)[153]	Vignette study	2L R/R LBCL	NR	EQ-5D-5L	Prolonged EFS: Mean (SD): 0.65 (0.32) Median (IQR): 0.7 (0.5—0.9) Progression: Mean (SD): 0.29 (0.46) Median (IQR): 0.4 (0.0—0.6)
NICE TA895[5]	CEA/CUA	Adult, transplant-intended patients with 2L DLBCL	Axi-cel vs. SOC	EQ-5D-5L (UK)	Event free: 0.785 Event free, after 5 years: Age 55 to 64: • Males: 0.833 • Females: 0.804 Age 65 to 74: • Males: 0.810 • Females: 0.760 Age 75+: • Males: 0.753 • Females: 0.692 Post Event: 0.71
NICE TA649[102]	CUA	Patients with R/R DLBCL who are ineligible for HSCT	Pola-BR vs. BR **Utilities sourced from TA559 (axi-cel; ZUMA-1 trial)*	EQ-5D-5L (5L-3L crosswalk applied) UK value set	Progression-free survival: 0.72 Progressive disease: 0.65

Abbreviations: 2L: second-line; ASCT: autologous stem cell transplantation; BR: bendamustine and rituximab; CEA: cost-effectiveness analysis; CUA: cost utility analysis; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; EQ-5D-5L: EuroQoL-5 dimensions-5 levels; HDCT: high dose chemotherapy; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; LBCL: large B cell lymphoma; R/R: refractory/relapsed; NOS: not otherwise specified; NR: not reported; SD: standard deviation; SE: standard error; SOC: standard of care; TA: technology appraisal; tFL: transformed follicular lymphoma; UK: United Kingdom..

B.3.4.4 Adverse reactions

As detailed in Section B.3.3.7, utility decrements were applied as a one-off decrement during Cycle 1 to estimate the reduction in HRQoL associated with short-term AEs.

Whilst EQ-5D-5L data were collected in TRANSFORM, utility decrements for individual AEs could not be calculated separately due to the limited number of AEs which coincided with the EQ-5D-5L data.[41] Instead, a multi-variate model was constructed using covariates of EFS events, Grade ≥3 AEs and lymphodepleting chemotherapy to derive an AE disutility for all Grade ≥3 AEs. In the base case, this utility decrement derived from TRANSFORM was used for all Grade ≥3 treatment-related AEs and for hypogammaglobulinemia (of any grade) and was applied for the average AE duration observed in the TRANSFORM trial of [redacted] days.[41] This excludes CRS and neurotoxicity for which different utility decrements were applied as detailed below.

CRS and neurotoxicity are serious AEs that may be associated with severe reductions in HRQoL. The utility decrements for these AEs were aligned with those used in TA895.[5] For CRS, this was considered to reduce overall HRQoL to 0, and therefore the utility decrement applied for CRS was set equal to the event-free health state utility value of 0.852.

The AE utility decrements applied in the base-case economic analysis are presented in Table 50.

Table 50: Summary of Grade ≥3 AE disutilities included in the economic model

AE	Utility decrement (SE)	Utility decrement source	Duration of AE (days)	Duration source
CRS	0.852	As per approach in TA895[5]	8.3	TA895[5]
Neurotoxicity	0.150	TA895[5]	40	TA895[5]
Hypogammaglobulinemia	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H [154]	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H[154]
Neutropenia				
Thrombocytopenia				
Anaemia				
Lymphopenia				
Febrile neutropenia				
Hypophosphatemia				
Leukopenia				
Prolonged cytopenia				
Infections				
Hypertension				

Abbreviations: AE: adverse event; DCO: data cut-off; SE: standard error.

B.3.4.5 Additional utility decrements

Lymphodepleting chemotherapy

Lymphodepleting chemotherapy was assumed to be associated with a utility decrement of [redacted], which was applied to 3 days, based on the TRANSFORM trial data. This decrement was applied

to all patients receiving 2L liso-cel. The utility decrement is also not applied for lymphodepleting chemotherapy received for 3L+ CAR-T therapy.

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

A number of potentially relevant HRQoL studies were identified via SLR, as detailed in Section B.3.4.3. However, as utility data were available from the TRANSFORM trial, which is directly relevant to the patient population of interest to this submission and includes patients receiving either liso-cel or SOC, the utility values from TRANSFORM were considered to represent the most appropriate source of utility data to inform the base case economic analysis.

In order to maximise the available sample size, treatment-independent utility values for the event-free and post-event health states were derived from the TRANSFORM trial data, while AE disutilities were then applied separately for patients receiving liso-cel and SOC, respectively.

A summary of the utility values used within the economic model is provided in Table 51. All health-state utility values are age-adjusted to account for the gradual change in utility due to the aging of the modelled cohort over time, in line with the NICE DSU recommended approach.[155] Alternative utility values based on those used in TA895 are considered in a scenario analysis, detailed in Section B.3.11.3.

It is assumed that patients who remain in the event-free health state after 5 years, would have their quality of life return to the age- and gender-matched general population values. The switch timepoint of 5 years is a conservative estimate, in line with TA895 and latest Committee preferences for CAR-T cell therapies.[5] A scenario analysis whereby this switch timepoint is 2 years is presented in Section B.3.11.3. An additional scenario analysis using the final health state utility values in TA895 was also explored.[104] Patients in the post-event health state are assumed not to return to general population utility values, given the extensive evidence in the literature relating to the long-term quality of life impact associated with ASCT and given that the majority of patients who are cured in the post-event health state are in the SOC arm (Section B.1.3.3).

Table 51: Summary of health-state utility values used in the base case economic analysis

Health state	Utility (Mean)	Source
Event-free	0.852	TRANSFORM EQ-5D analysis (final DCO; October 2023)[154]
Long-term remission	0.853[a]	
Post-event	0.808	

[a]Switch timepoint: 5.0 years.
Abbreviations: EQ-5D: EuroQoL-5 dimensions.

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

An economic SLR was conducted to identify cost and resource use studies conducted in patients with early relapsed/primary refractory LBCL. Full details of the SLR search strategy, study selection process and results are reported in Appendix I. No costing studies specific to the UK were identified.

The health economic analysis was conducted from the perspective of the NHS in England and therefore only included costs that would be incurred by the health system. Appropriate sources of unit costs, including NHS reference costs 2021–2022, the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT) were used to inform the cost inputs in the model, as described in more detail in the sections below. When relevant, no vial sharing is assumed when calculating the costs of treatments in the economic model.

B.3.5.1 Intervention and comparator costs and resource use

Liso-cel

CAR-T tariff

Following the evaluation of axi-cel in NICE TA895, a single CAR-T tariff cost of £41,101 was accepted by the Committee.[5] This single CAR-T tariff cost was assumed to include all costs of care from the decision for a person to have CAR-T therapy to 100 days after infusion, excluding CAR-T acquisition costs, bridging therapy costs, and any costs associated with the treatment of hypogammaglobulinemia (with IVIg). The CAR-T tariff therefore includes the costs of:

- **Pre-treatment:** Leukapheresis and lymphodepleting chemotherapy
- **Treatment:** Liso-cel drug administration costs
- **Post liso-cel infusion:** Resource use and AE management costs up to 100 days after infusion

Given the challenges associated with accurately costing the multiple components associated with the delivery of each liso-cel infusion, in the base-case economic model, all patients infused with liso-cel were assumed to accrue the single CAR-T tariff cost (£41,101), in addition to bridging therapy costs, any costs associated with the treatment of hypogammaglobulinemia (with IVIg), the drug acquisition cost of liso-cel, and any resource use required beyond the 100 days post-infusion. Costs associated with resource use beyond 100 days is described in Section B.3.5.3.

Whilst the CAR-T tariff was derived for axi-cel in TA895, liso-cel is anticipated to be associated with lower AE management costs compared with axi-cel. This is based on UK clinical expert feedback received as part of this submission, in addition to the results of a MAIC which report lower odds of key CAR-T cell-associated AEs with 2L liso-cel vs 2L axi-cel (see Section B.1.3.5).[45, 109] The CAR-T tariff cost of £41,101 is therefore likely to include an overestimation of the costs associated with the equivalent post-treatment AE management for liso-cel. A scenario analysis has been conducted whereby the costs of AEs associated with axi-cel and liso-cel are calculated separately to derive an adjusted CAR-T tariff cost for liso-cel. Details of this scenario analysis are presented in Section B.3.11.3.

The costs associated with bridging therapy and the acquisition cost of liso-cel are detailed below. The costs associated with the treatment of hypogammaglobulinemia (with IVIg) and resource use beyond the 100 days post-infusion are described in Section B.3.5.4 and Section B.3.5.3, respectively.

Pre-treatment

In the TRANSFORM trial (final DCO; October 2023), 1/92 (1.09%) patient received an out-of-specification liso-cel product.[41, 112] Costs associated with CAR-T acquisition for patients modelled to receive a non-conforming product were not accounted for, although administration costs were included, as the CAR-T tariff cost was applied to these patients.

Overall, [redacted]/92 ([redacted]) patients discontinued treatment prior to receiving lymphodepleting chemotherapy and did not receive infusion with liso-cel due to either manufacturing failure or non-measurable disease.[41] These patients were therefore assumed to accrue the costs of leukapheresis (presented in Table 53) and bridging therapy only (presented in Table 54). Following this, these patients were not assumed to accrue the costs associated with any 2L treatment, but instead go on to receive the relevant subsequent therapy costs of the liso-cel arm. The patient flow during the pre-treatment period for patients receiving liso-cel in the TRANSFORM trial is summarised below in Table 52.

Table 52: Patient flow during liso-cel pre-treatment period

	Liso-cel (TRANSFORM final DCO; October 2023)
Patients who undergo leukapheresis but do not receive CAR-T infusion	[redacted]
Patients who die prior to CAR-T infusion	[redacted]
Patients who receive planned treatment	96.74%
Patients who receive an out-of-specification CAR-T product	1.09%
Total	100%

Abbreviations: CAR-T: chimeric antigen T-cell therapy.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

Leukapheresis costs (applied to non-infused patients only)

As noted above, the granular leukapheresis costs applied for non-infused patients are presented below in Table 53.

Table 53: Granular leukapheresis costs (applied to non-infused patients only)

Item	Total cost	Source
Leukapheresis	£2,575.70	NHS Reference Costs 2021/22: SA43Z – Leukapheresis [Elective Inpatients][156]

Abbreviations: CAR-T: chimeric antigen T-cell therapy.
Source: NHS Reference Costs 2021/22.[156]

Bridging therapy costs

Whilst waiting for liso-cel manufacturing and infusion, patients may undergo a cycle of bridging chemotherapy or other treatments for disease control.[41, 132] The proportion of patients receiving

bridging therapy in the base case was based on the TRANSFORM trial (final DCO; October 2023) wherein 63% of patients received bridging therapy.[41]

The regimens received as part of bridging therapy were aligned with those received in the TRANSFORM trial and included R-GDP, R-DHAP and R-ICE.[41] Feedback from UK clinical experts was that these bridging therapies were generally aligned with UK clinical practice, where most patients would receive R-GDP, R-ICE or Pola-BR, in addition to radiotherapy and corticosteroids.[45] However, given the recent recommendation for Pola+R-CHP in 1L, it was highlighted by the clinical experts that the use of Pola-BR in 2L is likely to reduce substantially in the near future.[45, 84]

Based on this it was not considered appropriate to consider Pola-BR as part of bridging therapy and, for consistency with the majority of other model inputs for liso-cel, in the base case it was assumed that liso-cel patients would receive one cycle of bridging therapy based on the bridging therapy regimens received in the TRANSFORM trial (final DCO; October 2023).[41] A scenario analysis was conducted to explore the impact of 75% of patients receiving R-GDP and one third of patients receiving radiotherapy as bridging therapies, in line with UK clinical expert feedback which indicated that majority of patients receive R-GDP and radiotherapy.[45] As noted by clinicians, some patients may receive radiotherapy in combination with other immunochemotherapy regimens, thereby resulting in a bridging therapy distribution adding up to greater than 100%.[45]

All regimens were assumed to be given in an inpatient setting with the exception of R-GDP which was assumed to be given in an outpatient setting based on TA895 and supported by UK clinical expert feedback.[5, 45]

The same bridging therapy regimens for 2L liso-cel, based on the TRANSFORM trial, were applied to patients receiving axi-cel as a subsequent treatment in the 3L+ setting (see Section B.3.5.2) to align with the availability of chemotherapy-based bridging therapy in UK clinical practice. Unlike UK clinical practice, bridging therapy regimens were not administered in the ZUMA-1 trial prior to axi-cel infusion, and therefore distributions from ZUMA-1 could not be used to inform the model.[157]

The costs associated with the bridging therapy are detailed in Table 54. Bridging therapy drug acquisition costs were obtained from eMIT (2023) and, for weight-based therapies, the average dose required per administration was based on an average BSA of 1.92m^2 (from TRANSFORM).[41, 158] The cost of radiotherapy (used as part of bridging therapy in a scenario analysis only) is described in Table 60. Oral therapies were assumed to have no administration costs.

Each inpatient administration was assumed to cost £966.57 based NHS Reference Costs 2021/22: Weighted average of SA31 (A to F) Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's [Elective] (see Table 55). The administration of R-DHAP included the cost of two days of inpatient administration while the administration of R-ICE included the cost of three days of inpatient administration. A maximum of one administration cost was applied per day for inpatient treatments (regardless of the number of therapy administrations per day).

For R-GDP, each outpatient administration was assumed to include the cost of one "Complex chemotherapy, including prolonged infusional treatment" (£485.23) based on NHS Reference Costs 2021/22: SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional

Treatment, at First Attendance [Day case and regular day or night admissions], followed by three subsequent administrations of £383.54 each based on NHS Reference Costs 2021/22: SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle [Day case and regular day or night admissions] (see Table 55). A maximum administration cost was not applied for outpatient treatments, with each treatment incurring an administration cost regardless of the number of therapy administrations per day, in line with TA895.[5]

Table 54: Bridging therapy costs

Drug	Dosing regimen	Drug acquisition cost source	Drug acquisition cost per regimen	Administration cost per regimen[a]	Administration details	Total regimen cost	Proportion receiving (TRANSFORM final DCO; October 2023)
R-GDP							
Gemcitabine	1000 mg/m² IV on days 1 and 8	eMIT 2023 DKE033	£1,413.69	100% outpatient: £1,635.85	1 cycle; Each cycle consists of 1 prolonged infusion and 3 subsequent components	£3,049.52	[redacted]
Dexamethasone (Oral)	40 mg on days 1–4	eMIT 2023 DFC044					
Cisplatin	75 mg/m² IV on day 1	eMIT 2023 DHA010					
Rituximab	375 mg/m² IV on day 1	BNF Rixathon 100mg/10ml concentrate for solution for infusion[159]					
R-DHAP							
Dexamethasone (Oral)	See above	See above	£1,562.28	100% inpatient: £1,933.13	1 cycle; Each cycle consists of 2 inpatient days	£3,495.41	[redacted]
Cytarabine	2 x 2000 mg/m² on day 2	eMIT 2023 DHA023					
Cisplatin	See above	See above					
Rituximab	See above	See above					
R-ICE							
Carboplatin	AUC 5 (maximum 800 mg) IV on day 2	eMIT 2023 DHE002	£2,950.99	100% inpatient £2,899.70	1 cycle; Each cycle consists of 3 inpatient days	£5,850.69	[redacted]
Etoposide	100 mg/m² IV on days 1–3	eMIT 2023 DHA320					
Ifosfamide	5,000 mg/m² IV on day 2	BNF Ifosfamide 2g powder for					

		concentrate for solution for injection[160]					
Rituximab	See above	See above					

[a]Administration cost breakdown is summarised in Table 55 below.
Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; IV: intravenous.
Source: BNF 2023 (Ifosfamide);[160] BNF 2023 (Rixathon);[159] eMIT (2023).[158]

Table 55: Administration costs

Component	Cost	Source
Inpatient administration, per day visit	£966.57	NHS Reference Costs 2021/22: Weighted average of SA31(A to F) Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's [Elective]
Outpatient Complex chemotherapy, including prolonged infusional treatment	£485.23	NHS Reference Costs 2021/22: SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance [Daycase and Reg Day/Night]
Outpatient Subsequent elements of a chemotherapy cycle	£383.54	NHS Reference Costs 2021/22: SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle [Daycase and Reg Day/Night]

Abbreviations: NHS: National Health Service.
Source: NHS Reference Costs 2021/22.[156]

Liso-cel drug acquisition costs

Liso-cel is administered as a single infusion and the list price of one liso-cel infusion is £297,000.00. This includes the shipping, engineering and generation of the CAR-T cells. Within this submission a simple PAS discount of [redacted]% has been applied to the list price of liso-cel and therefore the PAS price for a single infusion is £[redacted].

SOC

The costs of SOC treatment were based on the drug acquisition and administration costs associated with the respective re-induction immunochemotherapies as well as HDCT and ASCT. In the TRANSFORM trial, 1/92 (1.1%) patient in the SOC arm did not receive SOC. In the base case, it was therefore assumed that patients in the SOC arm who were not modelled to receive SOC would not receive any 2L treatment costs and instead went on to receive the relevant subsequent therapy costs associated with the SOC arm.

Re-induction immunochemotherapy

Patients in the SOC arm were modelled to receive R-GDP, R-DHAP and R-ICE as re-induction chemotherapies, in line with the TRANSFORM trial (final DCO; October 2023).[41, 45 41] Feedback from UK clinical experts noted that the re-induction immunochemotherapy treatment distribution in the TRANSFORM trial was representative of UK clinical practice, with R-GDP and R-ICE being the main two regimens used in the UK. Therefore, and in order to align with the modelled efficacy data, the distribution of re-induction immunochemotherapy regimens as part of 2L SOC was based on the TRANSFORM trial.

Clinicians also provided their estimates on the distributions of re-induction immunochemotherapy based on their own clinical practice.[45] The clinical experts noted that regimens such as R-ESHAP, R-GEMOX and R-IVE are rarely used in clinical practice which aligns with the treatment distribution in the TRANSFORM trial.[45] The distribution of re-induction immunochemotherapies based on the TRANSFORM trial are detailed below in Table 56. A scenario analysis using clinician estimates of the distribution of re-induction immunochemotherapies was also explored and the results of this scenario are presented in Section B.3.11.3 below.

It was assumed that all chemotherapy regimens were delivered in the inpatient setting with the exception of R-GDP which was administered in the outpatient setting, per the approach taken for the same chemotherapy regimens used for bridging therapy in the liso-cel arm. The same administration costs incurred for bridging therapy for liso-cel were adopted for SOC.

HDCT and ASCT

In the TRANSFORM trial (13th May 2022 DCO), among patients in the SOC arm, 43/92 (46.7%) patients received HDCT and ASCT following re-induction immunochemotherapy.[114] HDCT was assumed to comprise the BEAM regimen and the costs associated with the administration of BEAM were assumed to be covered by the costs of ASCT. The drug acquisition costs of BEAM are presented in Table 56. A breakdown of the costs associated with ASCT is presented in Table 57.

Table 56: 2L SOC chemotherapy costs (excluding subsequent ASCT)

Drug	Dosing regimen	Drug acquisition cost source	Drug acquisition cost per regimen	Administration cost per regimen[a]	Administration details	Total regimen cost	Proportion receiving
2L SOC re-induction immunochemotherapy							
R-GDP							
Gemcitabine	1000 mg/m² IV on days 1 and 8 every 3 weeks for 3 cycles	eMIT 2023 DKE033	£4,241.06	100% outpatient £4,907.51	3 cycles; Each cycle consists of 1 prolonged infusion and 3 subsequent components	£9,148.57	[redacted]
Dexamethasone (Oral)	40 mg on days 1–4 every 3 weeks for 3 cycles	eMIT 2023 DFC044					
Cisplatin	75 mg/m² IV on day 1 every 3 weeks for 3 cycles	eMIT 2023 DHA010					
Rituximab	375 mg/m² IV on day 1 every 3 weeks for 3 cycles	BNF Rixathon 100mg/10ml concentrate for solution for infusion[159]					
R-DHAP							
Dexamethasone (Oral)	See above	See above	£4,686.83	100% inpatient £5,799.40	3 cycles; Each cycle consists of 2 inpatient days	£10,486.24	[redacted]
Cytarabine	2 x 2000 mg/m² on day 2 every 3 weeks for 3 cycles	eMIT 2023 DHA023					
Cisplatin	See above	See above					
Rituximab	See above	See above					
R-ICE							
Carboplatin	AUC 5 (maximum 800 mg) IV on day 2 every	eMIT 2023 DHE002	£8,852.96	100% inpatient		£17,552.07	[redacted]

	3 weeks for up to 3 cycles			£8,699.11	3 cycles; Each cycle consists of 3 inpatient days		
Etoposide	100 mg/m² IV on days 1–3 every 3 weeks for up to 3 cycles	eMIT 2023 DHA320					
Ifosfamide	5,000 mg/m² IV on day 2 every 3 weeks for up to 3 cycles	BNF Ifosfamide 2g powder for concentrate for solution for injection[160]					
Rituximab	See above	See above					
HDCT							
BEAM							
Carmustine	300 mg/m² IV on day 1 for 1 cycle	NICE NG52: NHL Diagnosis and Management. Costs inflated to 2021/2022 using NHS CII Pay & Price Index.[161]	£2,804.80	£0	Administration costs assumed to be covered by ASCT procedure, in line with TA895[5]	£2,804.80	[redacted]
Etoposide	200 mg/m² IV on days 2–5 for 1 cycle	eMIT 2023 DHA320					
Cytarabine	200 mg/m² IV on days 2–5 for 1 cycle	eMIT 2023 DHA023					
Melphalan	140 mg/m² IV on day 6 for 1 cycle (	eMIT 2023 DHA179					

[a]Administration cost breakdown is summarised in Table 55 above.
Abbreviations: ASCT: autologous stem cell transplant; BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; HDCT: high dose chemotherapy; IV: intravenous; NHL: Non-Hodgkin's Lymphoma; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; SOC: standard of care.
Source: BNF 2023 (Ifosfamide);[160] BNF 2023 (Rixathon);[159] eMIT (2023);[158] NICE NG52.[161]

Table 57: Breakdown of ASCT costs

Components	Proportion receiving ASCT	Cost	Source
Stem cell collection	46.7%	£5,808.35	NHS Reference Costs 2021/22: SA18 Bone Marrow Harvest.
ASCT, per patient		£37,624.50	NICE NG52: NHL Diagnosis and Management Appendix A. Costs inflated to 2021/2022 using NHSCII Pay & Price index.

Abbreviations: ASCT: autologous stem cell transplantation; NHS: National Health Service; NHSCII: NHS Cost Inflation Index; NICE: National Institute for Health and Care Excellence.
Source: NHS Reference Costs 2021/22;[156] NICE NG52.[161]

B.3.5.2 Subsequent therapies costs and resource use for all patients

The economic analysis assumed that patients may receive subsequent 3L+ therapies which include chemotherapies, CAR-T therapies and radiotherapy.

Application of subsequent therapy costs

All costs associated with subsequent therapies were applied as a one-off cost to the proportion of patients moving to their next treatment based on TTNT data from the TRANSFORM trial. However, a TTNT event could include either death (which was already accounted for in the OS curves) or progression to a subsequent treatment. Therefore, the percentage of TTNT events that are receipt of subsequent therapy was calculated using the number of patients receiving at least 1 subsequent treatment from TRANSFORM divided by the total number of TTNT events. These calculations are summarised in Table 58 below for the liso-cel and SOC arms.

Table 58: TTNT proportion calculations

Treatment arm	Number of patients receiving at least 1 subsequent treatment	Total number of TTNT events	Percentage of TTNT events that are receipt of subsequent therapy
Liso-cel	32	46	69.6%
SOC	65	69	94.2%

Abbreviations: SOC: standard of care; TTNT: time to next treatment.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

These percentages were applied to the TTNT extrapolation to calculate the total proportion of patients who received at least one subsequent treatment (liso-cel: [redacted]%; SOC: [redacted]%).

The distribution of subsequent therapies was based on TTNT data from the TRANSFORM trial (final DCO; October 2023), which are summarised in Table 59. As noted in Section B.3.2.4, the subsequent treatment distribution from the TRANSFORM trial does not fully reflect current UK clinical practice wherein patients now receive 3L+ bispecifics in place of chemotherapy, as per feedback from UK clinical experts.[45] It was not feasible to adjust the TRANSFORM OS data to account for this impact of routine availability of bispecifics or to use the clinician estimates of subsequent treatment distributions as it would bias the economic analysis against liso-cel by adjusting costs to align clinical practice without adjusting for efficacy. Therefore, it was deemed

most appropriate to model the subsequent treatment distribution in the base case economic model on the TRANSFORM trial data.

Nevertheless, as described in Section B.3.11.3, a scenario analysis was conducted to adjust for the differences in subsequent treatments between the TRANSFORM trial and UK clinical practice, both with respect to costs and efficacy. In this scenario analysis, the subsequent therapy distribution was based on that from UK clinical experts. More details are described in Section B.3.11.3.

Table 59: Subsequent therapies distribution used in the base case

Subsequent treatment option	Liso-cel	SOC
Proportion of patients who receive a subsequent treatment	[redacted]	[redacted]
ASCT	9.38%	0.00%
Allo-SCT	25.00%	3.08%
3L+ chemotherapy	100.00%	35.38%
3L+ CAR-T	0.00%	93.85%
3L+ radiotherapy	12.50%	0.00%

Note: The % of patients receiving each subsequent treatment may sum to over 100% as patients may receive more than one subsequent treatment.
Abbreviations: 3L+: third-line and beyond; Allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; SOC: standard of care.
Source: BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

ASCT, allo-SCT and radiotherapy

The cost of ASCT has been detailed previously in Table 57. The cost of allogeneic SCT and radiotherapy is presented below in Table 60.

Table 60: Breakdown of radiotherapy and allogeneic SCT costs

Components	Cost	Source
Radiotherapy	£243.33	NHS Reference Costs 2021/22: Weighted average of SC(21 to 28)Z, SC30Z, and SC31Z Radiotherapy
Allo-SCT	£39,541	NHS Reference Costs 2021/22: Weighted average of SA38A, SA39A, and SA40Z Peripheral Blood Stem Cell Transplant, Allogenic [Elective]

Abbreviations: Allo-SCT: allogeneic stem cell transplant; NHS: National Health Service.
Source: NHS Reference Costs 2021/22.[156]

Chemotherapy

For 3L+ chemotherapy, patients in the TRANSFORM trial received a wide range of chemotherapy regimens with many individual regimens being given to very small numbers of patients. Based on UK clinical opinion, the chemotherapy regimen received in 3L+ was assumed to be 100% R-bendamustine, delivered 100% in the outpatient setting. Costs associated with R-bendamustine are presented below in Table 61.

Only drug acquisition and administration costs were considered; no costs associated with AEs were considered for subsequent therapies.

Table 61: 3L+ chemotherapy costs

Drug	Dosing regimen	Drug acquisition cost source	Drug acquisition cost per regimen	Administration cost per regimen[a]	Administration details	Total regimen cost	Proportion receiving
R-bendamustine							
Bendamustine	90 mg/m² IV on days 1 and 2 of every 21-day cycle for 6 cycles. Infusion time: 30–60 minutes.	eMIT 2023 DZR015[158]	£5,417.30	100% outpatient £5,009.20	Maximum 6 cycles; Each cycle consists of 1 prolonged infusion and 3 subsequent components	£10,426.50	100%
Rituximab	375 mg/m² IV on day 1	BNF Rixathon 100mg/10ml concentrate for solution for infusion[159]					

[a] Administration cost breakdown is summarised in Table 55 above.
Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; IV: intravenous.

CAR-T therapy

For patients receiving 3L+ CAR-T therapy, this was assumed to be axi-cel. The patient flow for axi-cel during the pre-treatment period based on the 3L ZUMA-1 trial has been summarised in below. Similar to the approach taken for 2L liso-cel, any patients not receiving CAR-T infusion were assumed to receive the costs of leukapheresis and bridging therapy only. The costs associated with leukapheresis and bridging therapy have been detailed in Section B.3.5.1. Patients receiving 3L+ CAR-T were assumed to accrue the single CAR-T tariff cost (£41,101), bridging therapy costs (previously described in Table 54) and the drug acquisition cost of axi-cel (at list price: £280,451).[5] No costs associated with AEs were considered for subsequent therapies and therefore the cost of IVIg was not considered at 3L+.

Table 62: Patient flow during axi-cel pre-treatment period

	Axi-cel (as a subsequent therapy only) (ZUMA-1)
Patients who undergo leukapheresis but do not receive CAR-T infusion	6.31%
Patients who die prior to CAR-T infusion[a]	2.70%
Patients who receive planned treatment	90.99%
Patients who receive an out-of-specification CAR-T product	0.00%
Total	100%

[a] Patients who die prior to CAR-T infusion (relevant for 3L+ axi-cel only) were assumed to accrue the costs of leukapheresis and bridging therapy only.
Abbreviations: CAR-T: chimeric antigen receptor T-cell therapy.
Source: Neelapu *et al.* 2017.[157]; NICE TA872.[104]

B.3.5.3 Health state costs and resource use

The base-case economic model considered resource use (monitoring and follow-up) in both the 2L and 3L+ settings. Clinical expert feedback was sought to estimate the resource use costs for patients receiving liso-cel and SOC in 2L and the resource use costs for patients in 3L+.[45]

UK clinical experts were asked to estimate the frequency of resource use across 3 different time periods: 0–3 months, 3–12 months and 12 months plus in both the liso-cel and SOC arms.[45] For liso-cel, given the one-off CAR-T tariff is assumed to include all costs of care up to 100 days post-infusion, no additional resource use costs were included in the model for liso-cel patients in Months 0–3. Whilst 0–3 months is slightly <100 days, the assumption that additional resource use costs are accrued after Month 3 for patients in the liso-cel arm is therefore conservative. Similarly for SOC, given the high costs associated with ASCT and the inpatient administration of the majority of chemotherapy regimens, it was not considered that additional resource use costs would be necessary in the first 3 months.

Total resource use costs were calculated by multiplying the unit cost for each resource use element by the frequencies estimated by the clinical experts. After 5 years (60 months) for patients in both 2L and 3L+, it was assumed that resource use requirements would reduce to 2 GP visits per year, based on the same assumption made in TA895 and confirmation from UK clinical experts.

Table 63: Resource use estimates at 2L and 3L+

Resource use	2L							3L+	
	Liso-cel			SOC			All patients	All patients	
	0-3 months	3-12 months	12-60 months	0-3 months	3-12 months	12-60 months	60 months +	0-60 months	60 months +
Outpatient visit	N/A – all resource use within the first 100 days of liso-cel infusion are assumed to be included in the one-off CAR-T tariff cost	4.3	3.3	N/A – no additional resource use costs were assumed for SOC in the first 3 months	3.3	2.7		8.0	
Inpatient hospitalisation		2.3			0.7			4.0	
GP visit		1.0	1.7		1.0	1.7	2.0	4.0	2.0
Cancer nurse		4.7	0.7		2.0	0.7		4.0	
District nurse visits		0.7						4.0	
Bone marrow biopsy and/or aspirate		0.2						0.5	
Complete blood count		7.3	4.7		7.3	6.0		10.0	
Liver function test (LFT)		6.0	4.3		6.0	3.0		10.0	
Lactate dehydrogenase (LDH)		4.7	3.3		4.7	1.3		8.0	
Immunoglobulins		3.0	3.3		1.0	1.0			
PET scan		0.7			0.7			2.0	
Calcium phosphate		4.7	2.7		2.7	2.7		4.0	
Renal function		6.00	5.30		6.00	3.00		10.0	

Abbreviations: CAR-T: chimeric antigen receptor therapy; CT: computed tomography; GP: general practitioner; LDH: lactate dehydrogenase; LFT: liver function test; Liso-cel: lisocabtagene maraleucel; PET: positron emission tomography; SoC: standard of care.

Table 64: Resource use unit costs

Resource use	Unit cost	Unit cost source
Outpatient visit	£517.29	NHS Reference Costs 2021/22: Weighted average of SA31(A to F) Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's [Day case]
Inpatient days	£966.57	NHS Reference Costs 2021/22: Weighted average of SA31(A to F) Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's [Elective]
GP visit	£41.00	PSSRU 2022: Cost and unit estimations for a surgery consultation with GP
Cancer nurse	£119.00	NHS Reference Costs 2021/22: N10AF Specialist Nursing, Cancer Related, Adult, Face to face
District nurse visits	£53.74	NHS Reference Costs 2021/22: N02AF District Nurse, Adult, Face to face
Bone marrow biopsy and/or aspirate	£796.27	NHS Reference Costs 2021/22: Sum of SA33Z Diagnostic Bone Marrow Extraction and DAPS02 Histopathology and histology
Complete blood count	£2.96	NHS Reference Costs 2021/22: DAPS05 Haematology
Liver function test (LFT)	£10.82	NHS Reference Costs 2021/22: 7 * DAPS04 Clinical biochemistry
Lactate Dehydrogenase (LDH)	£1.55	NHS Reference Costs 2021/22: DAPS04 Clinical biochemistry
Immunoglobulins	£1.55	NHS Reference Costs 2021/22: DAPS04 Clinical biochemistry
PET scan	£362.55	NHS Reference Costs 2021/22: RN07A Positron Emission Tomography (PET), 19 years and over
Calcium phosphate	£10.82	NHS Reference Costs 2021/22: 7 * DAPS04 Clinical biochemistry
Renal function	£10.82	NHS Reference Costs 2021/22: 7 * DAPS04 Clinical biochemistry

Abbreviations: CAR-T: chimeric antigen receptor therapy; CT: computed tomography; GP: general practitioner; LDH: lactate dehydrogenase; LFT: liver function test; Liso-cel: lisocabtagene maraleucel; PET: positron emission tomography; SoC: standard of care.
Source: NHS Reference Costs 2021/22;[156] PSSRU 2022.[162]

B.3.5.4 Adverse event costs and resource use

AE costs considered within the economic model included the costs associated with the management of both treatment-related AEs and AESIs: cytokine release syndrome (CRS), neurotoxicity (NT) and hypogammaglobulinaemia.

Liso-cel AEs

As previously detailed in Section B.3.5.1, it was assumed that the CAR-T tariff cost includes the costs associated with management of post-infusion (treatment-related) AEs associated with liso-cel, the AEs of special interest CRS and neurotoxicity, with the exception of costs associated with IVIg for the management of hypogammaglobulinaemia.

SOC AEs

For SOC, the base-case economic model included the costs associated with the management of all Grade ≥3 AEs that occurred in ≥ 5% of patients in the TRANSFORM trial (DCO 23rd Oct 2023) as well as all grade AEs of special interest: CRS, neurotoxicity and hypogammaglobulinemia. The costs associated with the management of all Grade ≥3 treatment-related AEs are presented in Table 65. The costs associated with the management of all grade AEs of special interest are detailed in the following sections.

Table 65: Costs included with the model for the management of Grade ≥3 AEs that occurred in ≥ 5% of patients in the TRANSFORM trial (DCO Oct 2023) for SOC only

AE	Unit cost	Source
Neutropenia	£2,335.50	NHS Reference Costs 2021/22: Weighted average of SA35 (A to E) Agranulocytosis
Thrombocytopenia	£2,163.16	NHS Reference Costs 2021/22: Weighted average of SA12(G,H,J,K) Thrombocytopenia
Anaemia	£1,603.06	NHS Reference Costs 2021/22: Weighted average of SA09(G,H,J,K,L) Other Red Blood Cell Disorders
Lymphopenia	£1,772.97	NHS Reference Costs 2021/22: Weighted average of SA08(G,H,J) Other Haematological or Splenic Disorders
Febrile neutropenia	£2,335.50	NHS Reference Costs 2021/22: Weighted average of SA35(A to E) Agranulocytosis
Leukopenia	£1,772.97	NHS Reference Costs 2021/22: Weighted average of SA08(G,H,J) Other Haematological or Splenic Disorders
Prolonged cytopenia	£2,708.15	NHS Reference Costs 2021/22: Weighted average of SA01(G,H,J,K) Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia
Hypophosphatemia	£1,774.81	NHS Reference Costs 2021/22: Weighted average of KC04 (A,B) Inborn Errors of Metabolism
Infections	£1,943.23	NHS Reference Costs 2021/22: Weighted average of WJ03(A to G) Standard Infectious Diseases
Hypertension	£781.13	NHS Reference Costs 2021/22: EB04Z Hypertension

Abbreviations: AE: adverse event; DCO: data cut-off; SOC: standard of care.
Source: NHS Reference Costs 2021/22.[156]

AEs of special interest

CRS

Given the costs of CRS are assumed to be included within the one-off CAR-T tariff for liso-cel and zero patients in the SOC arm of TRANSFORM experienced any grade CRS (see Section B.3.3.7), the costs of CRS were not granularly calculated within the model.[41]

Neurotoxicity

The costs associated with the management of neurotoxicity were aligned with the neurotoxicity management guidance provided in the liso-cel SmPC.[132] Given the costs of neurotoxicity are assumed to be included within the one-off CAR-T tariff for liso-cel, the granular costs calculated

below were applied in the model to patients experiencing neurotoxicity in the SOC arm of the TRANSFORM trial only.[41]

The average length of ICU stay was assumed to be 3 days for Grade ≥3 neurotoxicity events, based on the TRANSFORM trial (DCO 23rd Oct 2023).[41] The average daily cost per ICU stay was based on the weighted average of SA31 (A to F): Malignant Lymphoma, including Hodgkin's and non-Hodgkin's in the NHS Reference Costs 2021–2022.[156] No drug administration costs were considered as it was assumed that all drugs would be administered as part of an inpatient stay. The costs included within the model for the management of neurotoxicity are presented in Table 66 below.

Table 66: Costs associated with neurotoxicity events (applied to SOC patients only)

Parameter	Daily ICU/ unit cost (£)	Duration/ total amount mg required	Total cost per neurotoxicity event	Source
Cost per neurotoxicity event, Grade 1–2			**£12.20**	
Dexamethasone	2.98 per 33 mg	13 mg	12.20	eMIT (2023)
Cost per neurotoxicity event, Grade ≥3			**£15,100.46**	
ICU admission	5,031.68	3 days	15,095.04	NHS Reference Costs 2021–2022: Weighted average of SA31A–F Malignant Lymphoma, including Hodgkin's and non-Hodgkin's
Dexamethasone	2.98 per 33 mg	135 mg	12.20	eMIT (2023)

Abbreviations: ICU: intensive care unit; SOC: standard of care.
Source: eMIT (2023);[158] NHS Reference Costs 2021/22.[156]

Hypogammaglobulinemia

The costs associated with the management of hypogammaglobulinemia with IVIg are summarised in Table 67 below. These costs are not assumed to be included within the one-off CAR-T tariff costs for liso-cel.

In the TRANSFORM trial, [redacted] of patients received IVIg treatment, which is higher than the total proportion of patients who experienced any grade of hypogammaglobulinemia in both arms of TRANSFORM (liso-cel: [redacted]; SOC: [redacted]).[41] This discrepancy is due to the TRANSFORM trial design, where IVIg treatment was given by investigator discretion. The eligibility criteria for receiving IVIg in TRANSFORM trial was therefore less stringent than criteria currently used in UK clinical practice, where guidance stipulates that patients must have hypogammaglobulinemia and IgG <4g/L, recurrent or severe bacterial infection and documented vaccine challenge.[163]

The model therefore applies the costs of IVIg treatment to the proportion of patients experiencing Grade ≥3 and Grade 1-2 hypogammaglobulinemia in TRANSFORM in both the liso-cel and SOC arms, in order to more closely align with UK clinical practice. This is still considered a conservative approach because in UK clinical practice patients would only receive IVIg if they also develop a recurrent or severe bacterial infection, meaning that only a subset of patients with hypogammaglobulinemia would be eligible to receive IVIg treatment in UK clinical practice. Given

more patients experienced a hypogammaglobulinemia event in the liso-cel arm, the current approach is expected to overestimate the costs of hypogammaglobulinemia management in the liso-cel arm versus UK clinical practice.

Table 67: Costs associated with hypogammaglobulinaemia treatment

Item	Proportion of patients	Cost per unit (£)	Dosing schedule	Drug costs per episode (£)	Administration cost per episode (£)	Management cost (£)	Duration	Total IVIg cost
IVIg for grade ≥3 hypogammaglobulinaemia	Liso-cel: [redacted] SOC: [redacted]	570.00 per 10,000 mg	500 mg/kg every 4 weeks	£28,764.69	£3,890.06	£1,351.34	11.4 months	**£34,006.09**
IVIg for grade 1–2 hypogammaglobulinaemia	Liso-cel: [redacted] SOC: [redacted]		400 mg/kg every 4 weeks	£9,083.59	£1,535.55	£39.23	4.5 months	**£10,660.14**

Abbreviations: IVIg: intravenous immunoglobulin; SOC: standard of care.
Source: BNF 2023 (IVIg);[164] BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[41]

B.3.5.5 Miscellaneous costs and resource use

End-of-life costs

Patients who die in the economic model prior to 5 years were assumed to incur a one-time terminal care cost of £10,687.00 during the model cycle. Patients who survive beyond 5 years were considered long-term survivors and therefore, were not assumed to accrue the costs of terminal care. The cost of terminal care was based on PSSRU hospital care estimates (2022).[162]

B.3.6 *Severity*

The severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the absolute and proportional severity modifiers.[165] The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022), as detailed in NICE TSD 23.[166, 167] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2018–2020.[139] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al.* (2022) through the NICE DSU.[155]

The baseline characteristics for the modelled population were informed by the TRANSFORM trial, as detailed in Table 68 below, and the total QALYs for the population of patients receiving SOC in UK clinical practice was informed by the results of the base case probabilistic economic analysis, where SOC was associated with [redacted] QALYs.

As shown in Table 69, the results of the severity modifier calculations demonstrate that liso-cel is not eligible for a severity modifier when compared to SOC.

Table 68: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Percentage female (%)	42.9%	Section B.3.3.1
Starting age (mean)	[redacted]	
Health state utility: EFS	[redacted]	Section B.3.4.6
Health state utility: Post-event	[redacted]	

Abbreviations: QALY: quality adjusted life years.
Source: TRANSFORM CSR (final DCO; October 2023).[41]

Table 69: Summary of QALY shortfall analysis

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	[redacted]	[redacted]	1

Abbreviations: QALY: quality-adjusted life year.

B.3.7 *Uncertainty*

There are three key areas of uncertainty in this appraisal, with further details on how this results in benefits not captured in the QALY calculation elaborated in Section B.3.13:

- **OS for patients in the SOC arm of the TRANSFORM trial is likely to be overestimated versus UK clinical practice:** For three reasons, OS is expected to be overestimated in the TRANSFORM trial:
    1. Patients were leukapheresed at the time of randomisation in the TRANSFORM trial, meaning that they were subsequently able to crossover and receive 3L+ CAR-T cell therapy within a median duration of [redacted], much faster than would be expected in UK clinical practice
    2. As patients were leukapheresed in the 2L setting, their T-cells were not subjected to 2L treatment, potentially leading to increased T-cell fitness and therefore improved outcomes with 3L+ CAR-T cell therapy than would be expected in UK clinical practice
    3. Of patients who received subsequent treatment in the TRANSFORM trial, 93.85% received 3L+ CAR-T cell therapy; clinicians expected this proportion would only be 66.25% in UK clinical practice[41, 45]
        - For these reasons, OS for the SOC arm is likely overestimated, with UK clinical experts indicating that all of the potential extrapolations for SOC OS were clinically implausible. While it is not possible to fully adjust for this, a scenario analysis has been conducted in Section B.3.11.3 which takes a weighted average of data from the TRANSFORM trial and the CORAL study to explore the impact of poorer OS outcomes for patients receiving SOC.
- **Patients in the TRANSFORM trial primarily received 3L+ chemotherapy unlike UK clinical practice wherein UK clinical experts indicated the majority of patients would receive novel 3L+ treatments, including bispecifics and antibody drug conjugates:[45]** Bispecific antibodies, such as glofitamab and epcoritamab, and antibody drug conjugates, such as loncastuximab tesirine, have recently been recommended for use in the UK, and are associated with improved efficacy outcomes compared to chemotherapy, which has historically been used in this setting.[103, 105, 106] However, very few patients received 3L+ bispecifics or antibody drug conjugates in the TRANSFORM trial. This means that the relative efficacy of liso-cel compared with SOC in this economic analysis is a conservative estimate and the efficacy of liso-cel in patients with early relapsed/primary refractory LBCL in clinical practice can therefore, be expected to be higher.
- **The CAR-T tariff cost of £41,101 is likely to overestimate the AE management costs associated with liso-cel:** The currently used CAR-T tariff cost of £41,101, was estimated based on axi-cel as part of TA872 and TA895. Liso-cel is associated with a more favourable safety profile when compared to axi-cel, particularly for high-grade neurotoxicity, which would translate to lower ICU usage associated with liso-cel.[45, 47] While the true tariff cost associated with liso-cel is unknown, it is likely that the currently used cost of £41,101 overestimates the cost of AE management associated with liso-cel, meaning the results of the base case economic analysis are conservative. A scenario analysis has been conducted in Section B.3.11.3 using a reduced tariff cost for liso-cel to attempt to account for this difference.

B.3.8 *Managed access proposal*

This submission [redacted] a proposal for managed access – the liso-cel data in this submission are based on the final DCO from the TRANSFORM trial and no further data are expected to become available in this patient population to inform decision making.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of the key inputs used in the base case analysis is presented in Table 70.

Table 70: Summary of key base-case analysis inputs applied in the economic model

Variable	Value			Section in submission
Model settings				
Discount rate (costs and benefits)	3.5%			Section B.3.2.2
Time horizon	Lifetime			
Patient baseline characteristics				
Mean age, years	[redacted]			Section B.3.3.1
Proportion of female patients, %	42.9			
Mean body weight, kg	[redacted]			
Mean BSA, m^2	[redacted]			
Survival inputs				
	EFS	**OS**	**TTNT**	
Extrapolation for Liso-cel	Log-normal	Log-normal	Log-normal	Section B.3.3.3 (OS) Section B.3.3.4 (EFS) Section B.3.3.5 (TTNT)
Extrapolation for SOC	Log-normal	Log-normal	Log-normal	
Health-state utility values				
Event-free	0.852			Section B.3.4.6
Long-term remission (switch timepoint 5 years)	0.853[a]			
Post-event	0.808			
Adverse event rates				
	Liso-cel (n=92)[a]		**SOC (n=91)**	
CRS (any grade)	48.9%		0.0%	Section B.3.3.7
CRS (Grade ≥3)	1.1%		0.0%	
Neurotoxicity (any grade)	10.9%		[redacted]	
Neurotoxicity (Grade ≥3)	4.3%		[redacted]	

Hypogammaglobulinemia (any grade)	[redacted]	[redacted]	
Hypogammaglobulinemia (Grade ≥3)	[redacted]	[redacted]	
Neutropenia	81.5%	51.6%	
Thrombocytopenia	50.0%	68.1%	
Anaemia	52.2%	56.0%	
Lymphopenia	26.1%	9.9%	
Febrile neutropenia	[redacted]	[redacted]	
Leukopenia	16.3%	13.2%	
Prolonged cytopenia	43.5%	3.3%	
Hypophosphatemia	[redacted]	[redacted]	
Infections	15.2%	20.9%	
Hypertension	[redacted]	[redacted]	
Adverse event utility decrements (duration: days)			
	Utility decrement (SE)	**Duration of AE (days)**	
CRS	0.852	8.3	Section B.3.4.4
Neurotoxicity	0.150	40	
Hypogammaglobulinemia	[redacted]	[redacted]	
Neutropenia			
Thrombocytopenia			
Anaemia			
Lymphopenia			
Febrile neutropenia			
Hypophosphatemia			
Leukopenia			
Prolonged cytopenia			
Infections			
Hypertension			
Lymphodepleting chemotherapy	[redacted]	3	Section B.3.4.5
Liso-cel costs			
	Distribution		
Patients who undergo leukapheresis but do not receive CAR-T infusion	2.17%		Section B.3.5.1
Patients who die prior to CAR-T infusion	0.00%		
Patients who receive planned treatment	96.74%		
Patients who receive an out-of-specification CAR-T product	1.09%		

Patients who undergo leukapheresis but do not receive CAR-T infusion	2.17%			
CAR-T tariff cost				
CAR-T tariff cost	£41,101.00			Section B.3.5.1
Bridging chemotherapy				
	Distribution		**Total regimen cost**	
R-GDP (1 cycle)	[redacted]		£3,049.52	Section B.3.5.1
R-DHAP (1 cycle)	[redacted]		£3,495.41	
R-ICE (1 cycle)	[redacted]		£5,850.69	
2L SOC costs				
HDCT (BEAM)	[redacted]		£2,804.80	Section B.3.5.1
R-GDP (3 cycles)	[redacted]		£9,148.57	
R-DHAP (3 cycles)	[redacted]		£10,486.24	
R-ICE (3 cycles)	[redacted]		£17,552.07	
ASCT – stem cell collection	46.7%		£5,808.35	
ASCT – cost per patient			£37,624.50	
Subsequent therapies				
	Liso-cel	**SOC**	**Total regimen cost**	
ASCT	9.38%	0.00%	N/A See above	Section B.3.5.2
Allogenic SCT	25.00%	3.08%	£39,541	
3L+ radiotherapy	12.50%	0.00%	£243.33	
3L+ chemotherapy	100.00%	35.38%	As per 2L SOC – See above	
3L CAR-T	0.00%	93.85%	£280,451 (+ CAR-T tariff and bridging therapy costs – See above)	
Resource use frequencies (2L)				
	Liso-cel		**SOC**	
	3-12 months	**12-60 months**	**3-12 months**	**12-60 months**
Outpatient visit	4.3	3.3	3.3	2.7
Inpatient hospitalisation	2.3		0.7	
GP visit	1.0	1.7	1.0	1.7
Cancer nurse	4.7	0.7	2.0	0.7
District nurse visits	0.7			
Bone marrow biopsy and/or aspirate	0.2			

Complete blood count	7.3	4.7	7.3	6.0	
Liver function test (LFT)	6.0	4.3	6.0	3.0	
Lactate dehydrogenase (LDH)	4.7	3.3	4.7	1.3	
Immunoglobulins	3.0	3.3	1.0	1.0	
PET scan	0.7		0.7		
Calcium phosphate	4.7	2.7	2.7	2.7	
Renal function	6.00	5.30	6.00	3.00	
Resource use frequencies 2L and 3L+					
	All Patients (2L)		**All patients (3L+)**		
	60 months+		**0-60 months**	**60 months+**	
Outpatient visit			8.0		Section B.3.5.3
Inpatient hospitalisation			4.0		
GP visit	2.0		4.0	2.0	
Cancer nurse			4.0		
District nurse visits			4.0		
Bone marrow biopsy and/or aspirate			0.5		
Complete blood count			10.0		
Liver function test (LFT)			10.0		
Lactate dehydrogenase (LDH)			8.0		
Immunoglobulins					
PET scan			2.0		
Calcium phosphate			4.0		
Renal function			10.0		
Resource use costs					
Outpatient visit	£517.29				Section B.3.5.3
Inpatient days	£966.57				
GP visit	£41.00				
Cancer nurse	£119.00				
District nurse visits	£53.74				
Bone marrow biopsy and/or aspirate	£796.27				
Complete blood count	£2.96				
Liver function test (LFT)	£10.82				
Lactate Dehydrogenase (LDH)	£1.55				
Immunoglobulins	£1.55				
PET scan	£362.55				
Calcium phosphate	£10.82				
Renal function	£10.82				

AE costs		
Neutropenia	£2,335.50	Section B.3.5.4
Thrombocytopenia	£2,163.16	
Anaemia	£1,603.06	
Lymphopenia	£1,772.97	
Febrile neutropenia	£2,335.50	
Leukopenia	£1,772.97	
Prolonged cytopenia	£2,708.15	
Hypophosphatemia	£1,774.81	
Infections	£1,943.23	
Hypertension	£781.13	
Neurotoxicity Grade 1–2	£12.20	
Neurotoxicity Grade ≥3	£15,100.46	
IVIg for hypogammaglobulinaemia Grade ≥3	£34,006.09	
IVIg for hypogammaglobulinaemia Grade 1–2	£10,660.14	
End-of-life care costs		
End-of-life care costs	£10,687.00	Section B.3.5.5

[a] As previously detailed in Section B.3.5.1, it was assumed that the CAR-T tariff cost includes the costs associated with management of post-infusion (treatment-related) AEs associated with liso-cel, the AEs of special interest CRS and neurotoxicity, with the exception of costs associated with IVIg for the management of hypogammaglobulinaemia.

Abbreviations: AE: adverse event; ASCT: allogenic stem-cell transplant; CAR-T: chimeric antigen T-cell; CT: computed tomography; EFS: event-free survival; GP: general practitioner; HSUVs: health state utility value; IVIg: intravenous immunoglobulin; LDH: lactate dehydrogenease; LFT: liver function test; Liso-cel: lisocabtagene maraleucel; OS: overall survival; PET: positron emission tomography; Pola + BR: polatuzumab vedotin, bendamustine, rituximab; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, cisplatin, dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; TTNT: time to next treatment; SOC: standard of care.

B.3.9.2 Assumptions

A summary of assumptions in the economic analysis can be found in Table 71 below.

Table 71: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Clinical effectiveness		
3L+ efficacy	The outcomes from the TRANSFORM SoC arm, where patients received liso-cel at 3L+, are assumed to reflect the outcomes for 3L+ patients in the UK, where patients receive axi-cel	The appropriateness of this assumption is supported by the results of a MAIC by Maloney *et al.* (2021), which compared the efficacy of 3L+ liso-cel, using data from the TRANSCEND trial (based on the 17.5 months DCO), versus 3L+ axi-cel, using data from the ZUMA-1 trial.[47] After matching and adjusting for clinically relevant prognostic factors, the HRs between liso-cel and axi-cel for PFS and OS were 0.81 (95% CI: 0.44, 1.49) and 0.95 (95% CI: 0.58, 1.57), respectively.[47] These results support the assumption of equivalence between 3L+ liso-cel and 3L+ axi-cel in the model.
Non-conforming product	Efficacy of patients receiving liso-cel outside of the product specification (n=1) is assumed to be the same as that in those receiving a liso-cel conforming product	This assumption is based on evidence from the TRANSCEND trial, investigating liso-cel for patients with 3L R/R LBCL, which demonstrated that efficacy was similar between those receiving conforming and nonconforming products. Specifically, a comparison of the KM data for the full efficacy analysis set and for patients receiving outside of specification product in TRANSCEND show similar PFS and OS between these two groups.[168] Furthermore, the model is informed by available data from the TRANSFORM trial, which inherently captures the efficacy data for the one patient who received an out of specification product.
Bridging therapy distributions	Bridging therapy distributions from the TRANSFORM trial were used to inform the distributions in the model	The bridging therapy received in the TRANSFORM trial included R-GDP, R-DHAP and R-ICE.[41] Feedback from UK clinical experts was that these bridging therapies were generally aligned with UK clinical practice and all had similar efficacy. It was therefore considered most appropriate to use the bridging therapy treatment distributions from TRANSFORM trial to inform the model for costing purposes.
3L+ treatment distributions	Subsequent treatment distributions from the TRANSFORM trial were used to inform the 3L+ treatment distribution in the model	Clinicians consulted as part of this submission agreed that the subsequent treatment distributions were generally representative of the UK clinical practice but noted that patients would primarily receive bispecifics or an antibody drug conjugate at 3L+ instead of chemotherapy following the recent NICE recommendations for glofitamab (TA927), loncastuximab tesirine (TA947) and epcoritamab (TA954) within the last 12 months.[105, 106]

		The availability of these bispecific treatments would likely result in marked improvements in efficacy for patients requiring a subsequent treatment following liso-cel, compared to the chemotherapy regimens used in the TRANSFORM trial. However, there are no plausible mechanisms that could be used to adjust the OS KM data from the TRANSFORM trial in order to account for this. Therefore, it was considered inappropriate to model the costs associated with 3L+ bispecifics, when it would not be possible to equally account for their improved efficacy. Doing so would heavily bias the economic analysis against liso-cel – since patients in the TRANSFORM trial were able to receive CAR-T cell therapy after SOC in the TRANSFORM trial, which is aligned with UK clinical practice (although UK clinical experts separately indicated that SOC in the TRANSFORM trial is overestimated). Therefore, the only appropriate approach is to use the subsequent treatment distributions in the model based on the TRANSFORM trial for costing purposes, to reflect the efficacy data applied in the model.
Survival models		
Modelling approach	Mortality of cured patients is equal to that of the age- and sex-adjusted general population, with an SMR-adjustment of 1.09	An SMR of 1.09, derived from the publication by Maurer (2014), was used in the base case to adjust for excess mortality in long-term survivors.[129] This approach was validated with UK clinical experts and was in line with previous appraisals of CAR T-cell therapies, including the 3L+ DLBCL appraisals and TA895.[5, 133] Assuming the same excess mortality as per the 3L+ indication is considered a conservative approach, given this 2L population will have better prognosis compared to the more heavily treated 3L+ patients
Extrapolations	Extrapolations of OS, EFS and TTNT are based on mixture cure models, as detailed further in Section B.3.3	The appropriateness of mixture cure models is evidenced by the plateaus observed in both EFS, TTNT and OS data from TRANSFORM, which are indicative of a proportion of patients with early relapsed/primary refractory LBCL experiencing long-term remission and survival. The use of MCMs has also been deemed appropriate in previous NICE CAR-T appraisals such as TA895 and TA872 in R/R DLBCL and TA554 in R/R ALL whereby patients who survive beyond five years were considered to be effectively cured.[5, 104, 133] Moreover, as noted in TA895, a validation study by Vadgama *et al.* (2022) of survival models using follow-up data of five years from the ZUMA-1 trial found that the mixture cure models most accurately and reliably predicted the long-term survival for DLBCL patients treated with axi-cel compared to spline-based and standard parametric models, further supporting the appropriateness of mixture models for CAR-T therapies in this indication.[5, 142]
Utility values		
Health state utility values	Health state utility values are assumed to be equal between the liso-cel and SOC arms for all health states, based on data from the TRANSFORM trial.	For consistency with the source of clinical inputs included in the model for liso-cel and SOC, and the relevance of data from the TRANSFORM trial to the patient population of interest and the decision problem of this submission, the utility values used in the base case analysis were based on EQ-5D data from the TRANSFORM trial. The approach to not include treatment-specific utility values is considered a conservative assumption, as this means that the HRQoL decrement resulting from the physical and psychological burden associated with SOC is unlikely to be captured adequately in the economic model. Alternative utility values sourced from TA895 were explored in scenario analysis.

Utility for cured patients	Quality of life for long-term survivors, remaining in the event-free health state returns to that of the age- and gender-matched general population values after 5 years, reflective of the fact that patients would be effectively cured.	This assumption was applied to both the liso-cel and SOC arms and is in line with previous CAR T appraisals.[5, 127, 134] The timepoint of five years was chosen to align with the previous 2L appraisal for axi-cel (TA895), where the five year timepoint was accepted by the EAG and is a more conservative estimate compared to earlier CAR-T appraisals.
Costs		
Resource use costs	The CAR-T tariff was assumed to include all relevant costs for liso-cel pre-infusion and post-infusion for 100 days with the exception of bridging therapy and IVIg. Additional resource use costs were applied after 3 months.	The assumptions for the CAR-T tariff were adopted based on those accepted in TA895.[5] Given the more favourable safety profile associated with liso-cel compared with axi-cel as per the results of a MAIC by Maloney *et al.* 2021, it is likely that the CAR-T tariff based on the axi-cel appraisal is an overestimation of the equivalent costs associated with liso-cel.[47] Clinician feedback received as part of this submission noted that the liso-cel has a more favourable safety profile compared with axi-cel, particularly for high-grade neurotoxicity which would translate to lower ICU usage associated with liso-cel.[45] Clinicians noted that this is applicable to the use of liso-cel at both 2L and 3L+ settings.[45] As such, a scenario analysis was conducted where the CAR-T tariff was adjusted to separately reflect the AE costs associated with liso-cel and axi-cel, as detailed in Section B.3.11.3.
	No additional resource use costs were applied between 0-3 months for SOC.	It was assumed that any resource use required by patients receiving SOC would already be captured in the administration costs associated with ASCT and inpatient chemotherapy, and therefore no additional resource use costs were included for patients receiving SOC in the first 3 months as a simplifying assumption. It is plausible that patients may require additional costs not captured in the model – such as additional monitoring tests – which would mean that this assumption is conservative.
Costs for cured patients	After 5 years, patients in any health state are assumed to receive reduced resource use costs	For this analysis, costs were aligned with the most recent EAG preferences in TA895 where it is assumed that patients at 5 years would incur the cost of 2 GP visits per year.[5] In addition, it was assumed that these patients would not receive EOL costs, as after 5 years, these patients are considered cured and therefore any deaths after this timepoint would not be due to the original disease.

Abbreviations: 2L: second line; 3L: third line; 3L+: third line and beyond; ALL: acute lymphoblastic leukaemia; EAG: external assessment group; EFS: event-free survival; EQ-5D: EuroQol-5 dimensions; HR: hazard ratio; CAR-T: chimeric antigen receptor-T cell; DLBCL: diffuse large B-cell lymphoma; GP: general practitioner; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; MAIC: matching-adjusted indirect comparison; MCM: mixture cure model; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; SMR: standardised mortality ratio; SoC: standard of care; TA: technology appraisal; TTNT: time to next treatment.

B.3.10 *Base-case results*

Results of the economic analysis are presented in Section B.3.10.1 below.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for liso-cel (with PAS) versus SOC are presented in Table 72 and Table 73, respectively.

Liso-cel was found to be a cost-effective use of NHS resources when compared with SOC at a WTP threshold of £30,000/ QALY in both the deterministic and probabilistic analyses. At PAS price in the deterministic base case, liso-cel is associated with [redacted] more QALYs at a reduced cost of [redacted] when compared with SOC. As a result, liso-cel at PAS price was dominant compared with SOC. These analysis were performed with a PAS for liso-cel and all other modelled treatments were at list price.

Table 72: Deterministic base-case results (liso-cel PAS price)

Treatment	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	NHB at £20,000/QALY WTP threshold	NHB at £30,000/QALY WTP threshold
Liso-cel	[redacted]	10.29	[redacted]	[redacted]	1.50	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	8.78	[redacted]	-					

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Table 73: Probabilistic base-case results (liso-cel PAS price)

Treatment	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	NHB at £20,000/QALY WTP threshold	NHB at £30,000/QALY WTP threshold
Liso-cel	[redacted]	10.32	[redacted]	[redacted]	1.50	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	8.82	[redacted]	-					

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

B.3.10.2 Disaggregated results of the base case incremental cost-effectiveness analysis

Disaggregated results of the deterministic base case are presented in Table 74 to Table 76 below. The equivalent disaggregated results of the probabilistic base case are presented in Appendix J.

Table 74: Deterministic base case disaggregated QALYs by health state

Health state	QALY Liso-cel	QALY SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L treatment-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; QALY: quality-adjusted life year; SOC: standard of care

Table 75: Deterministic base case disaggregated costs by health state

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; SOC: standard of care.

Table 76: Deterministic base case disaggregated costs by resource type

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Primary treatment acquisition cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary treatment administration cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment administration cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE management and IVIG (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (EF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (Post-event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; EF: event-free; IVIG: intravenous immunoglobulin; SOC: standard of care.

B.3.11 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. Key assumptions in the model were explored in several scenario analyses which have been presented in Section B.3.11.3. Overall, the results of the sensitivity analyses conducted show that the base case results were found to be robust to uncertainty in key model inputs and assumptions and all relevant uncertainties have been adequately accounted for.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 500 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, the model assumes 10% of the mean value represents the SE.

The INHB convergence plots for liso-cel at PAS price are presented in Figure 53 below which demonstrate that the cumulative INHB stabilised after approximately 300 iterations.

Figure 53 : INHB convergence plot : liso-cel (PAS price) versus SOC

Abbreviations: PAS: patient access scheme; SOC: standard of care.

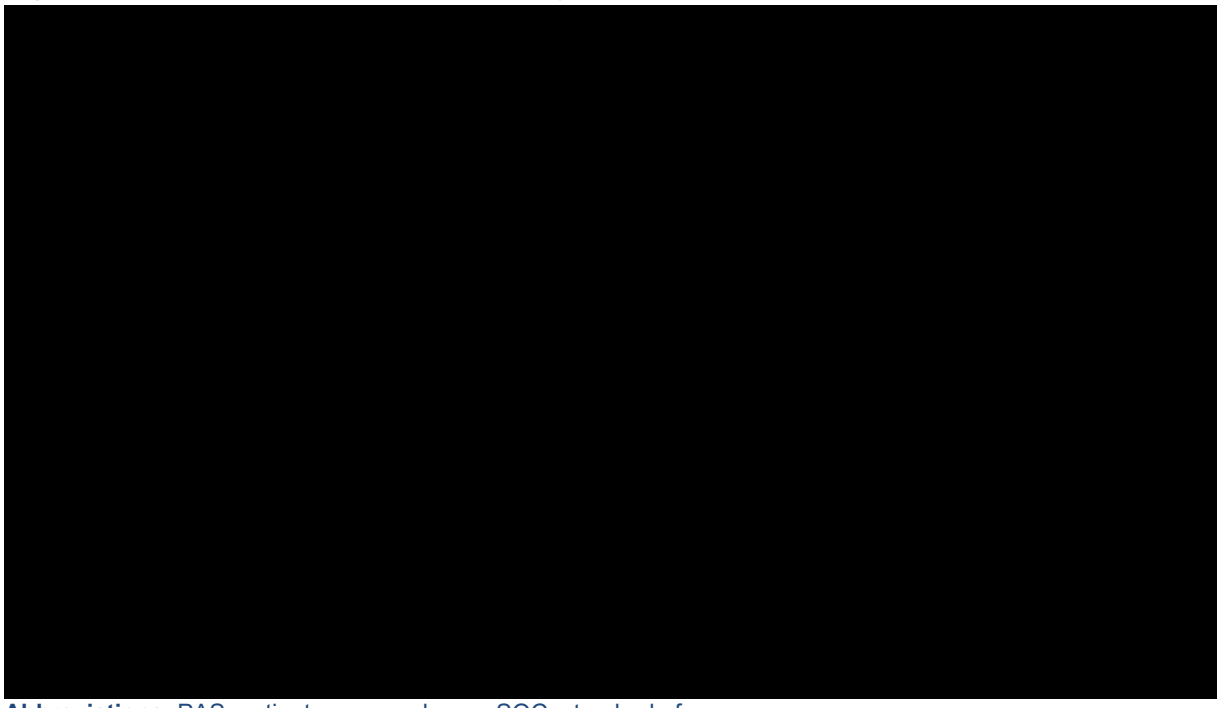
The scatter plot showing the incremental costs and QALYs for liso-cel at PAS price compared with SOC is presented in Figure 54, respectively. The majority of iterations (%) fall in the southeast quadrant, where liso-cel is dominant compared to SOC. The iterations in the southwest quadrant of the cost-effectiveness plane represent extreme scenarios within the range of uncertainty, and are not considered plausible, because they indicate liso-cel would result in fewer QALYs compared to SOC.

Figure 54: Cost-effectiveness plane: liso-cel (PAS price) versus SOC

Footnotes: The cost-effectiveness plane includes a WTP of £30,000/QALY.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care; WTP: willingness-to-pay.

Cost-effectiveness acceptability curves for liso-cel at PAS price when compared with SOC are presented in Figure 55, respectively. At a WTP threshold of £20,000 and £30,000 per QALY gained and using a PAS for liso-cel and list price for all other modelled treatments, the PSA found the probability of liso-cel being a cost-effective use of NHS resource to be [redacted]% and [redacted]%, respectively.

Figure 55: Cost-effectiveness acceptability curve: liso-cel (PAS price) versus SOC



Abbreviations: PAS: patient access scheme; SOC: standard of care.

B.3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSAs) were conducted to assess the robustness of the base case cost-effectiveness results by varying the input for each parameter in the model, whilst keeping all other inputs the same. For certain parameters where SEs of the mean were available, the lower and upper limits were defined by the 95% CI around the mean. In the absence of 95% CI, the inputs were arbitrarily varied by ±10%.

The tornado diagram showing the top 10 most influential parameters on ICER for liso-cel at PAS price versus SOC is presented in Figure 56. The parameters with the greatest impact on the ICER were the proportion of patients receiving a subsequent treatment in the SOC arm, the proportion of patients getting a successful axi-cel infusion and the proportion of patients receiving 3L CAR-T in the SOC arm. The decrease/increase in the ICER from the base case was less than £10,000 per QALY gained for all other parameters varied in the DSA.

Figure 56: Tornado diagram of the ten most influential parameters from the DSA: liso-cel (PAS price) versus SOC

Abbreviations: DSA: deterministic sensitivity analysis; PAS: patient access scheme; SOC: standard of care.

B.3.11.3 Scenario analysis

As noted in Section B.3.11, scenario analyses were conducted to explore the impact of assumptions and alternative inputs on the results of the cost-effectiveness model. The complete list of scenario analyses explored and their rationale are outlined below. All scenarios were run probabilistically.

None of the scenario analyses changed the cost-effectiveness conclusions of the base case analysis – liso-cel remained dominant versus SOC in all analyses. As such, scenario analysis results are also provided for incremental net health benefit (INHB) and change from baseline in costs, QALYs and INHB to aid interpretation. For all scenarios explored, liso-cel was associated with a positive INHB versus SOC, meaning liso-cel provides more QALYs at the given WTP threshold. Furthermore, the changes in INHB compared to the base case were generally minor, demonstrating that the base case results are associated with minimal uncertainty. These analyses were performed with a PAS for liso-cel and all other modelled treatments were at list price.

Of particular note, Scenarios 4 and 5 highlight the potentially conservative nature of the base case analysis, which is based on the TRANSFORM trial which, for the reasons detailed throughout this submission, potentially underestimates the ‘true’ OS associated with liso-cel, and overestimates the true OS associated with SOC.

In Scenario 4, which uses a more optimistic curve for liso-cel (Weibull) to more closely reflect UK clinical practice where patients can now receive more effective 3L+ bispecific therapies that were not available in TRANSFORM, there is a positive impact on the incremental QALYs and an increase in the INHB versus the base case of 0.23. In Scenario 5, where SOC OS is adjusted to better align with UK clinical practice, the incremental QALYs increase versus the base case and as a result the INHB shows an even larger increase of 0.54 compared to the base case.

Notably, in Scenario 13, which attempted to adjust for the differences in subsequent treatments between the TRANSFORM trial and UK clinical practice with respect to both costs and efficacy, there is a decrease in the INHB versus the base case (-0.37). However, this scenario should be interpreted with caution as this scenario does not account for any PAS discounts for the subsequent therapies and therefore the incremental costs are highly uncertain. The incremental QALYs are associated with less uncertainty and demonstrate a sizeable increase in the incremental QALYs versus the base case. This further suggests the base case economic analysis may be conservative, and the magnitude of cost-effectiveness for liso-cel is increased when adjustments are made to attempt to more closely replicate UK clinical practice. It should be noted that while this scenario uses a slightly more optimistic OS curve for liso-cel, the Weibull curve is still very similar to the base case extrapolation, and is unlikely to adequately capture the true improvement in OS that would be expected to result from the introduction of novel therapies, such as bispecifics, into UK clinical practice for patients who do require a subsequent treatment following liso-cel.

Table 77: Scenario analyses

Model element	Base case	Scenario analysis	Justification
EFS extrapolations	• Liso-cel (based on EFS data from TRANSFORM): **Log-normal**	1. Liso-cel (based on EFS data from TRANSFORM): **Log-logistic**	• Once the generalised gamma was excluded due to clinical implausibility, the log-normal extrapolation provided the best statistical fit alongside a cure fraction in line with UK clinical expert estimates, and therefore was used in the base case for liso-cel EFS (Section B.3.3.3). • The log-logistic extrapolation provided the next best statistical fit and also provided a cure fraction in line with UK clinical expert estimates, and therefore was considered as an alternative curve selection in this scenario analysis.
	• SOC (based on EFS data from TRANSFORM): **Log-normal**	2. SOC (based on EFS data from TRANSFORM): **Generalised Gamma**	• The log-normal curve was selected in the base case, as a curve with the second best statistical fit, to align with the curve choice for liso-cel based on the guidance provided in NICE TSD 14 (Section B.3.3.3). • The best fitting Generalised Gamma extrapolation was considered as an alternative curve selection in this scenario analysis.
OS extrapolations (liso-cel)	• Liso-cel (based on OS data from TRANSFORM): **Log-normal**	3. Liso-cel (based on OS data from TRANSFORM): **Generalised gamma**	• The log-normal extrapolation provided the best statistical fit to the observed OS data from TRANSFORM, and was considered clinically plausible based on UK clinical expert opinion, therefore, was selected in the base case. • The Generalised Gamma and Weibull extrapolations were both considered in scenario analyses to explore the selection of curves which resulted in slightly lower and higher cure fractions, respectively, compared to the base case log-normal extrapolation.
		4. Liso-cel (based on OS data from TRANSFORM): **Weibull**	
OS extrapolations (SOC)	• SOC (based on OS data from TRANSFORM): **Log-normal**	5. SOC (based on EFS data from TRANSFORM 66.25%/CORAL 33.75%): Log-normal/Gamma	• All of the SOC OS curves based on the TRANSFORM trial data were considered to substantially overestimate SOC OS by UK clinical experts. Therefore, to generate more plausible OS outcomes for OS, this scenario utilised a weighted average of the SOC OS curve from the TRANSFORM trial, and an SOC OS curve based on the CORAL trial. The CORAL trial investigated outcomes for SOC in this patient population prior to the availability of 3L+ CAR-T cell therapies, so may more accurately reflect the OS outcomes for patients receiving SOC who do not go onto receive 3L+ CAR-T cell therapy with axi-cel.[144]

			• SOC OS in CORAL was modelled based on the (non-Generalised) Gamma MCM. The Gamma MCM was the second-best fitting extrapolation; the best fitting log-logistic extrapolation was ruled out based on clinical plausibility, as it predicted that [redacted]% of non-cured patients would be alive a 2 years, which was not considered to be clinically plausible for a population of patients who could not receive CAR-T cell therapy at either 2L or 3L+. Further details of the CORAL extrapolations and rationale for the curve selection are provided in Appendix R. • The weighted average SOC OS curve used in this scenario analysis comprised of 66.25% of the liso-cel SOC OS extrapolation from TRANSFORM, and 33.75% of the CORAL OS extrapolation. These percentages were based on the assumption that TRANSFORM is representative of patients receiving 3L+ CAR-T and CORAL is representative of patients not receiving 3L+ CAR-T. In UK clinical practice, approximately 66.25% of patients would be expected to receive 3L+ CAR-T cell therapy following liso-cel, and the remaining 33.75% of patients would not. • The resulting OS extrapolation is associated with a 5 year survival of [redacted] (compared to [redacted]% in the base case), and a 10 year survival of [redacted] (compared to [redacted]% in the base case). UK clinical experts estimates that they would only expect 32.5% of patients to be cured following treatment with SOC in UK clinical practice, meaning that this scenario may still be conservative, and overestimate SOC OS when compared to UK clinical practice.
TTNT extrapolations	• Liso-cel (based on TTNT data from TRANSFORM): **Log-normal**	6. Liso-cel (based on TTNT data from TRANSFORM): **Log-logistic**	In the base case, once the Generalised gamma was excluded for clinical plausibility, the best fitting log-normal extrapolation was selected to model TTNT for liso-cel (Section B.3.3.5). The next best fitting log-logistic extrapolation was explored as an alternative curve selection in this scenario analysis.
	• SOC (based on TTNT data from TRANSFORM): **Log-normal**	7. SOC (based on TTNT data from TRANSFORM): **Log-logistic**	The log-normal extrapolation was selected as one of the best fitting extrapolations and for consistency with the chosen TTNT extrapolation for liso-cel, in line with the guidance provided in NICE TSD 14 (Section B.3.3.5). The log-logistic extrapolation was explored as an alternative curve selection in this scenario analysis.
Utility values	In the base case, health-state utility values were derived	8. HSUVs were based on the final HSUVs accepted in TA895:	TRANSFORM was considered to represent the most appropriate source of HSUVs for the base case economic analysis, as the TRANSFORM trial directly reflects the patient population and decision problem of relevance to this

	from EQ-5D data from the TRANSFORM trial: • Event-free: **0.852** • Long-term remission: **0.853** • Post-event: **0.808**	• Event-free: **0.785** • Long-term remission: **0.853** • Post-event: **0.720**	appraisal. However, to explore the impact of alternative HSUVs, the final HSUVs accepted as part of TA895 were explored in a scenario analysis. In this scenario analysis, event-free and post-event utilities of 0.785 and 0.720 were applied, derived from the ZUMA-7 and ZUMA-1 trials, respectively, in line with the committee's preferred assumptions as part of TA895. In line with the base case economic analysis, patients who remained event-free health state for 5 years or longer were assumed to return to general population utility.
Cure timepoint	**5 years.** At which point, any patients in the EFS state at 5 years return to general population utility, reduced resource use [1 GP visit every 6 months] and no end-of-life costs	9. **2 years.** At which point, any patients in the EFS state at 2 years return to general population utility, reduced resource use [1 GP visit every 6 months] and no end-of-life costs	Based on UK clinical expert opinion, it is assumed that most patients who remain event-free for two years would be considered cured. As a conservative assumption, in the base case economic analysis, it is assumed that all patients who remain in the event-free health state for 5 years are considered cured – this scenario explores the impact of this happening at 2 years, rather than 5 years.
CAR-T costs	The one-off CAR-T tariff cost is applied to all patients who receive 2L liso-cel infusion or 3L+ axi-cel infusion	10. AE costs calculated separately and an adjusted CAR-T tariff cost is used for 2L liso-cel (£38,424.69) and 3L+ axi-cel (£41,433.90), based on the costs associated with the AEs of both treatments	Liso-cel is associated with a more favourable safety profile when compared to axi-cel, with significantly lower odds of all-grade and Grade ≥3 CRS and study-specific neurological events.[47] Therefore, the application of the same CAR-T tariff cost to both liso-cel and axi-cel, which is assumed to capture the costs associated with AEs, is conservative. Therefore, this scenario adjusts the CAR-T tariff, to first remove the costs of axi-cel AEs based on the ZUMA-7 trial (assuming that the CAR-T tariff was based on axi-cel as a second-line treatment option). AE costs are then separately re-added for liso-cel (based on TRANSFORM) and axi-cel (based on the 3L+ ZUMA-1 trial), resulting in adjusted CAR-T tariff costs of £38,424.69 (for liso-cel) and £41,433.90 (for axi-cel). Further details on these AE frequencies and costs used in this scenario are provided in Appendix Q. This scenario therefore more accurately reflects the cost savings associated with the favourable safety profile of liso-cel compared to axi-cel.

Bridging therapy distribution	Distribution of bridging therapy regimens based on TRANSFORM for both 2L liso-cel infusion or 3L+ axi-cel infusion	11. Distribution of bridging therapy regimens based on clinical expert feedback for both 2L liso-cel infusion or 3L+ axi-cel infusion (75% of patients get R-GDP; one third get radiotherapy)	In the base case, the distribution of bridging therapy regimens is based on the TRANSFORM trial, to align with the modelled efficacy data. This scenario analysis explores an alternative distribution of bridging therapies (both for liso-cel and patients receiving subsequent treatment with axi-cel), where it was assumed that 75% of patients receive R-GDP as a bridging therapy, and one third of patients receive radiotherapy. This was to more closely with align with UK clinical practice where, based on UK clinical expert opinion, R-GDP usage is increasing because it can be delivered in the outpatient setting and hospital beds are limited.
SOC distribution	Distribution of 2L SOC based on that observed in TRANSFORM	12. Distribution of 2L SOC costs based on UK clinical expert feedback	In the base case, the distribution of chemotherapy regimens as part of 2L SOC was based on the TRANSFORM trial, in order to align with the modelled efficacy data. In this scenario analysis, an alternative distribution was explored based on UK clinical expert feedback, excluding treatments that were estimated to be received by <3% of patients as a simplifying assumption. Therefore, in this scenario analysis, 81.7% of patients were assumed to receive R-GDP, and 18.3% of patients were assumed to receive R-ICE.
Subsequent therapies	Distribution of subsequent therapies for liso-cel and SOC based on those received in TRANSFORM (2L)	13. Distribution of subsequent therapies for liso-cel and SOC based on UK clinical expert input. In addition, in this scenario the Weibull curve is chosen for liso-cel OS extrapolation based on TRANSFORM, and the Log-normal/Gamma curve is chosen for the SOC OS extrapolation (based on 66.25% TRANSFORM/33.75% CORAL)	For the reasons previously detailed throughout this submission, there is reason to believe that the results of the TRANSFORM trial underestimate OS for liso-cel and overestimate OS for SOC, compared to the results that would be expected in UK clinical practice. • Liso-cel OS in TRANSFORM is likely to be underestimated versus UK clinical practice, given the introduction of novel bispecifics as 3L+ treatment options in the UK. UK clinical experts estimated that the majority of patients (64.5%) would receive 3L+ treatment with glofitamab or epcoritamab if they required a subsequent treatment after liso-cel – only one patient received either epcoritamab or glofitamab in the TRANSFORM trial. The majority of patients received 3L+ treatment with chemotherapy regimens, which are associated with significantly worsened outcomes versus novel bispecific therapies. • At the same time, SOC OS in TRANSFORM is likely to be overestimated versus UK clinical practice, given that all patients were apheresed prior to randomisation, allowing patients to receive 3L+ CAR-T more quickly than they would after SOC in UK clinical practice, while their T-cells may be healthier (Section B.2.12.3)[47]

This scenario analysis attempted to adjust for the differences in subsequent treatments between the TRANSFORM trial and UK clinical practice, both with respect to costs and efficacy.

Therefore, in this scenario analysis, subsequent treatment distributions following liso-cel and SOC were based on UK clinical expert opinion, as detailed below.

Table 78: Summary of subsequent treatment distributions based on UK clinical expert opinion

Subsequent Treatment	Liso-cel	SoC
ASCT	1.25% (0%, 5%)	1.25% (0%, 5%)
Allo-SCT	3.75% (0%, 5%)	3.00% (0%, 5%)
R-GDP	2.97%	2.32%
R-DHAP	2.47%	1.94%
R-ICE	9.56%	7.49%
Axi-cel	0.00%	66.25% (40%, 85%)
Pola-BR	10.00% (5%, 20%)	9.25% (2%, 20%)
Glofitamab	32.50% (25%, 40%)	20.00% (5%, 30%)
Loncastuximab Tesirine	6.25% (5%, 10%)	5.50% (2%, 20%)
Epcoritamab	32.50% (25%, 40%)	20.00% (5%, 30%)
Radiotherapy	17.50% (5%, 25%)	11.75% (2%, 20%)

Abbreviations: Allo-SCT: allogenic stem cell transplant; ASCT: autologous stem cell transplant; Pola + BR: polatuzumab vedotin, bendamustine, rituximab; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, cisplatin, dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; SOC: standard of care.

A summary of the costs associated with each of the subsequent treatments is provided in Appendix R.

			To reflect the differences in efficacy that would be associated with the alternative subsequent treatment distributions, the following changes were made to the modelling approach for OS for both liso-cel and SOC: **Liso-Cel OS** • Liso-cel OS was based on the Weibull extrapolation, resulting in a slightly higher cure fraction of [redacted]%, compared to [redacted]% for the log-normal curve used in the base case. It is likely that this is still conservative, given that UK clinical experts expect that approximately 65% of patients would receive treatment with epcoritamab or glofitamab, compared with [redacted] patient who received either treatment in the TRANSFORM trial. • Therefore, the use of the Weibull curve for liso-cel OS in this scenario analysis is still conservative, as it effectively assumes that the introduction of bispecific antibodies in the 3L+ setting only results in an additional [redacted]% of patients being cured, compared to conventional chemotherapy regimens. However, there are no plausible alternatives to allow for adjustment of the liso-cel OS curve to truly reflect the improved OS outcomes that would likely be associated with the introduction of novel bispecific antibodies in this setting. **SOC OS** • As previously described in Scenario #5, all of the SOC OS curves from TRANSFORM were considered to overestimate OS, when compared with UK clinical practice. Therefore, in this scenario designed to best reflect UK clinical practice, the weighted average SOC OS curve derived from TRANSFORM/CORAL previously described in Scenario #5 was also used to model OS for SOC in this scenario analysis.

Abbreviations: 2L: second-line; 3L+: third-line and beyond; AE: adverse event; EFS: event-free survival; GP: general practitioner; HSUVs: health state utility value; MCM: mixture cure model; OS: overall survival; Pola + BR: polatuzumab vedotin, bendamustine, rituximab; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, cisplatin, dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; TTNT: time to next treatment; SOC: standard of care.

Table 79: Summary of scenario analysis results (probabilistic)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	Dominant	2.55			
1	EFS extrapolation (liso-cel): log-logistic	[redacted]	[redacted]	Dominant	2.55	-£41	0.00	0.00
2	EFS extrapolation (SOC): generalised gamma	[redacted]	[redacted]	Dominant	2.55	£15	0.01	0.01
3	OS extrapolation (liso-cel): generalised gamma	[redacted]	[redacted]	Dominant	2.74	-£28	0.19	0.19
4	OS extrapolation (liso-cel): Weibull	[redacted]	[redacted]	Dominant	2.78	-£38	0.23	0.23
5	OS extrapolation (SOC): TRANSFORM/CORAL mix	[redacted]	[redacted]	Dominant	3.08	£118	0.54	0.54
6	TTNT extrapolation (liso-cel): log-logistic	[redacted]	[redacted]	Dominant	2.54	£46	0.00	0.00
7	TTNT extrapolation (SOC): log-logistic	[redacted]	[redacted]	Dominant	2.55	-£54	0.00	0.00
8	Utility values: TA895	[redacted]	[redacted]	Dominant	2.70	£0	0.15	0.15
9	Cure timepoint: 2 years	[redacted]	[redacted]	Dominant	2.56	-£479	0.00	0.02
10	CAR-T costs: adjusted CAR-T tariff	[redacted]	[redacted]	Dominant	2.64	-£2,882	0.00	0.10
11	Bridging therapy distribution: UK clinical expert opinion	[redacted]	[redacted]	Dominant	2.52	£822	0.00	-0.03
12	SOC distribution: UK clinical expert opinion	[redacted]	[redacted]	Dominant	2.43	£3,606	0.00	-0.12
13	Subsequent therapies: Distribution based on UK clinical expert opinion, Weibull curve for liso-cel OS and SOC OS based on TRANSFORM/CORAL (using log-normal and gamma curves, respectively)	[redacted]	[redacted]	Dominant	2.18	£34,057	0.77	-0.37

Abbreviations: EFS: event-free survival; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYs: life years; OS: overall survival; QALYs: quality-adjusted life years; TTNT: time to next treatment; SOC: standard of care.

B.3.12 *Subgroup analysis*

No subgroups were considered relevant to this appraisal and as such, no subgroup analyses were included in the cost-effectiveness analysis.

B.3.13 *Benefits not captured in the QALY calculation*

Avoidance of futile burden associated with current 2L SOC

Given the potentially curative nature of liso-cel, a CAR-T therapy, and the detrimental side-effects of the current 2L SOC treatment (chemotherapy plus SCT), the QALY calculation does not fully capture the significant benefit for patients receiving a one-time curative treatment infusion at 2L, thereby avoiding the futile burden of the side-effects should the patient progress and receive 3L+ CAR-T. The emotional burden associated with intensive chemotherapy and the psychological impact of having a relapse were both noted in the patient organisation submission and consultation comments received as part of the axi-cel appraisal in 2L DLBCL (TA895):

Emotional burden associated with intensive chemotherapy

"Patients described feeling shocked and heartbroken when they heard their cancer had relapsed. One patient described the 'paralysing fear' they experienced when returning to hospital for a check-up, only to find out that the disease had come back. They discussed the difficulty of their treatment and the fear of having to go through 'gruelling' chemotherapy again." (p4, Patient organisation submission comments received from Anthony Nolan).[169]

"A Consultant Haematologist we spoke to stated that "patients diagnosed with DLBCL reaching second line treatment face a significant challenge: having an intense treatment that fails in up to 75% of cases. This is three out of four transplant-eligible patients in second line are subjected to a futile treatment… Because of this, some patients see 2L treatment like a toll they need to pay to get to CAR-T cell therapy." In addition to side effects from intense rounds of chemotherapy combined with the possibility of treatment failure has a significant emotional burden on patients and carers" (p5, Patient organisation submission comments received from Blood Cancer UK).[169]

"We are concerned NHS patients will continue to receive intensive 2nd line chemotherapy which is destined to fail in more than 80% of patients. Clinically it is hard to justify subjecting patients to toxicity of intensive chemotherapy which is quite likely to fail when a better therapeutic alternative is available. The psychological impact of having to go through a treatment which is quite likely to fail has not been considered fully." (p.3, Consultation comments received in TA895).[170]

Psychological impact associated with experiencing relapse

"Another spoke about feeling knocked back by their relapse, after believing they had made real progress through extremely difficult treatment cycles, they described feeling 'back at square one' in their treatment journey." (p.4, Patient organisation submission comments received from Anthony Nolan).[169]

Therefore, the emotional burden on both patients and carers due to the psychological impact of cancer relapse and gruelling nature of chemotherapy with a high risk of failure cannot be understated. As the economic analysis presented as part of this submission assumes treatment-independent utilities and subsequent AE disutilities experienced are assumed to be transient in nature, the true emotional burden of current 2L SOC treatment for patients with early refractory/primary relapsed LBCL is unlikely to have been captured adequately by the QALY calculation. The introduction of liso-cel as a 2L treatment option is anticipated to bring significant benefits to patients' emotional wellbeing and quality of life. The curative nature of liso-cel would further alleviate feelings of uncertainty associated with the potential of failure of chemotherapy on top of the taxing side-effects.

The introduction of liso-cel as a 2L treatment for early refractory/primary relapsed LBCL would therefore optimise the treatment pathway, thereby enabling patients to receive an effective and curative 2L CAR-T treatment option and eliminate the need to undergo intensive chemotherapy and ASCT, which are associated with detrimental side effects and a high risk of failure. The use of CAR-T therapy at 2L may also further improve outcomes compared to use at 3L+ and would avoid NHS England incurring costs of both 2L ASCT and 3L+ CAR-T therapy.

Downstream impact of liso-cel as a 2L treatment option

Whilst axi-cel, a similar CAR-T curative therapy, has been recommended as a 3L+ treatment option for R/R DLBCL patients, axi-cel has been found to have a higher incidence of CRS and neurotoxicity compared to liso-cel and therefore, liso-cel would be better tolerated by patients.[47] This translates to both an improvement in HRQoL as well as minimisation of healthcare resource use required for the management of these AEs which tend to be resource intensive, with an increased burden on patients and carers. The downstream impact of liso-cel as a 2L treatment is hence, significant but has not been fully captured in the current base case economic analysis. However, a scenario analysis attempting to adjust the CAR-T tariff cost to reflect the reduced AEs associated with liso-cel compared to axi-cel demonstrated that the base case economic analysis may be conservative. It should be noted that this adjustment may not fully capture the lower costs associated with liso-cel because no breakdown of the costs included in the CAR-T tariff have been provided. As such, this adjustment only changes AE costs but further resource savings may also be associated with liso-cel that have not been accounted for in this scenario. For example, no adjustment has been made to account for the increased potential for outpatient delivery of liso-cel as a result of the improved safety profile, when compared to axi-cel.

Conservative estimate of the true efficacy of liso-cel due to differences between the TRANSFORM trial and UK clinical practice which overestimate the efficacy of SOC and underestimate the efficacy of liso-cel

As noted in Section B.3.7, the efficacy of liso-cel in patients with early relapsed/primary refractory LBCL as a 2L therapy based on the TRANSFORM trial data is a conservative estimate of its true efficacy due to differences between the trial and UK clinical practice.

In TRANSFORM all patients were apheresed before randomisation, meaning the patients who did not respond to SOC received liso-cel in a median of [redacted].[41] This does not align with UK clinical practice, where patients would undergo apheresis and CAR-T manufacture only after progression on 2L treatment. There would therefore be more delay between progression on 2L treatment and subsequent receipt of 3L+ CAR-T in UK clinical practice compared to the 15-day

period seen in the TRANSFORM trial. This aligned with clinician feedback received as part of this submission which indicated that the proportion of patients who received SOC treatment in the TRANSFORM trial who proceeded to receive liso-cel as a 3L+ therapy (93.85%) is higher than the estimated proportion of patients receiving 3L+ axi-cel treatment in UK clinical practice (66.2%).[45] The overestimation of OS for patients who received SOC would result in the underestimation of incremental QALYs for patients who received liso-cel.

Clinicians noted that the OS for patients receiving liso-cel in the TRANSFORM trial was underestimated as patients primarily received chemotherapy unlike UK clinical practice where patients who were not cured at 2L would receive bispecifics at 3L+ and therefore, have a greater survival benefit.[45] The benefits of bispecifics as an effective 3L+ treatment option cannot be captured in the economic model. Overall, the relative efficacy of liso-cel compared with SOC in this economic analysis is a conservative estimate and would similarly underestimate the incremental QALYs for liso-cel.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Face validity of model inputs in line with UK clinical practice in early relapsed/primary refractory LBCL

Model validations were performed in alignment with best practices.[171] A thorough validation process was conducted with health economic and UK clinical experts in LBCL to inform the survival extrapolations, treatment pathway, generalisability of evidence sources and model inputs in order to inform the derivation and selection of base case extrapolations used in the economic analysis.

Feedback received from the validation meeting exercises was written up in a clinical validation meeting report which is included in the reference pack accompanying this submission. Key feedback received from the clinical experts informed the economic modelling and where possible, UK sources were used for model inputs with similar inputs and approaches to prior CAR-T appraisals were adopted as well.[5, 104]

Technical validity of model programming

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks), based on the published TECH-VER checklist,[172]

were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

The TRANSFORM trial investigated the efficacy of liso-cel in a high risk population of patients with 2L early relapsed/primary refractory LBCL. The results demonstrated that liso-cel drives clinically meaningful and more durable responses compared SOC, resulting in statistically significant improvements in EFS. At the time of the final DCO (October 2023), the stratified EFS HR of 0.38 (95% CI: 0.26, 0.54) indicates that liso-cel is associated with a 62% reduction in the risk of experiencing disease progression, death, an inadequate response to treatment or the start of a new antineoplastic therapy versus SOC. These EFS results translated into improvements in OS that demonstrate the curative potential of liso-cel. For patients who experience the deepest responses to treatment; the stratified OS HR was 0.76 (95% CI: 0.48, 1.19) indicating that liso-cel reduces the hazard of death by 24% when compared to SOC.

These compelling efficacy results were reflected in the base case probabilistic economic analysis, where liso-cel was associated with a substantially increased [redacted] LYGs and [redacted] QALYs when compared to SOC. These results underscore the potential for liso-cel to improve both the quality and duration of life for patients with early relapsed/primary refractory LBCL, who otherwise face the prospect of having to endure treatment with SOC before they are able to access the transformative benefits of CAR-T cell therapy at later lines of treatment – although unfortunately some patients will die or would not otherwise be fit enough to be able to receive 3L+ treatment after SOC.

Based on these results, in the base case probabilistic and deterministic analyses, liso-cel was shown to represent a cost-effective treatment option when compared to SOC; at PAS price, liso-cel was found to be dominant versus liso-cel in both the deterministic and probabilistic analyses. Thus, liso-cel can be considered a cost-effective use of NHS resources in 2L patients with early relapsed/primary refractory LBCL.

The PSA found the probability of liso-cel being cost-effective to be [redacted]% and [redacted]% at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The DSA results identified a small number of key influential parameters – primarily, inputs determining the proportion of patients receiving treatment with either liso-cel, ASCT or axi-cel (in the 3L+ setting). This is to be expected, given the high acquisition costs associated with these treatments, however, these inputs are informed by data from the robust the TRANSFORM and ZUMA-1 trials and therefore should not be considered to represent major sources of uncertainty. Regardless, liso-cel was dominant versus SOC in all DSA scenarios considered.

Importantly, these economic results omit important benefits that cannot be captured in the QALY. Most notably, the base case OS extrapolations are likely to overestimate OS for SOC and underestimate OS for liso-cel, resulting in conservative base case economic results. While it is not possible to fully adjust for these differences, the results of Scenario 13 demonstrate that the true magnitude of cost-effectiveness for liso-cel versus SOC is likely to be greater than the base case results. In this scenario analysis, which attempts to adjust both costs and efficacy to align more closely with UK clinical practice, liso-cel was associated with a sizeable increase in

incremental QALYs, and while the NHB decreases when all subsequent treatments are at list prices, this scenario is likely to increase the magnitude of cost-effectiveness when the confidential PAS discounts for axi-cel and other relevant subsequent treatments are incorporated.

Strengths

A robust clinical validation exercise was conducted by BMS with four clinical experts and two health economic experts in the UK in order to validate the key inputs and assumptions in the model, including monitoring frequencies, utility inputs, subsequent treatment options as well as to elicit plausible long-term survival estimates. The results of the economic analysis are therefore considered highly relevant to decision-making for the introduction of liso-cel into NHS clinical practice.

Additionally, a strength of the economic analysis is that axi-cel has recently been appraised by NICE, and a review of TA895 was conducted during model design and development, and thus it was possible to take into account a number of learnings from this previous appraisal, and the current base case economic analysis for liso-cel has aimed to align with as many of the committee's preferred assumptions from TA895 as possible. Furthermore, the model closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully captured and discounting costs and benefits at a rate of 3.5% per annum.

Comparison versus axi-cel

While SOC is the most appropriate comparator for this submission, it is important to recognise that a significant proportion of the patient population being considered in this submission would, in reality, receive axi-cel, which is currently available through the Cancer Drugs Fund (CDF) on a time-limited basis. As such, it is important to consider the potential implications of liso-cel displacing the use of axi-cel in this patient population.

Firstly, axi-cel is only available for patients with DLBCL and HGBCL, meaning patients with PMBCL and FL3B cannot access a 2L CAR-T cell therapy.[5] For early relapsed/primary refractory PMBCL and FL3B patients, 2L treatment is currently limited to re-induction immunochemotherapy and subsequent HDCT and ASCT; the introduction of liso-cel to the treatment pathway at 2L would therefore substantially improve outcomes for these patients.

Secondly, it is important to highlight that the design of the TRANSFORM trial more closely reflects UK clinical practice compared to the ZUMA-7 trial that informed TA895. In the TRANSFORM trial, bridging chemotherapy included immunochemotherapy, per UK clinical practice. In contrast, the ZUMA-7 trial only permitted corticosteroids as a bridging chemotherapy. In TA895, clinical experts commented this may have made clinicians less likely to enrol patients with fast-progressing disease in the trial and thus introduced uncertainty in applicability of the survival outcomes estimated from ZUMA-7 to UK clinical practice. [4, 5] Clinical experts in TA895 also noted this may have resulted in a reduced incidence of Grade 3 or more CRS and neurotoxicity in ZUMA-7 compared to UK clinical practice.[5] In contrast, during the axi-cel appraisal, clinicians commended the TRANSFORM trial for its greater relevance to UK practice, which suggests that the cost-effectiveness assessment for liso-cel is associated with a higher degree of certainty compared to that of axi-cel.[5]

Moreover, it is worth noting that axi-cel was assessed for cost-effectiveness at a higher ICER threshold of £50,000 because it met the end-of-life criteria at the time of submission. The removal of this criteria from the NICE appraisal process means liso-cel will be evaluated at a lower ICER threshold, the maximum being £30,000 per QALY. Consequently, if recommended, liso-cel would likely represent a more cost-effective option compared to axi-cel and the displacement of axi-cel would lead to cost-savings for NHS England.

The cost savings are likely to be compounded by the fact that liso-cel is associated with a more favourable safety profile compared to axi-cel, which has significant implications for both patient QoL and healthcare resource utilisation.[109] For instance, managing CRS grade ≥ 3 was previously estimated to cost £6,900 as part of TA895 based on the cost of tocilizumab and assuming 4 days in the intensive care unit (ICU).[5] Reducing this cost would therefore be of significant benefit to the NHS, especially considering the capacity constraints the NHS is currently facing. In addition to cost savings, the favourable safety profile for liso-cel is also anticipated to translate to improved QoL for patients. Patients experiencing CRS grade ≥ 3 are typically modelled to have a quality of life of zero, reflecting the severity of this AE which greatly impairs or completely eliminates the patients' ability to lead a normal, functioning life during this period.[110] Furthermore, as a result of the favourable safety profile, liso-cel has a greater potential to be administered in the outpatient setting, which could further significantly reduce healthcare resource utilisation compared to axi-cel.[173] This increased potential for outpatient delivery would not only improve patient convenience and quality of life but also further reduce the burden on hospital resources and lead to cost savings for the healthcare system.

The favourable safety profile of liso-cel and ease of administration may be attributed to the additional complexity in its manufacturing process. Specifically, the manufacture of liso-cel involves a dual train approach to manufacturing CD4 and CD8 cells, ensuring a consistent 1:1 ratio in every liso-cel infusion unlike other CAR-T products (see Section B.1.2). This innovative approach to CAR-T cell production may contribute to the observed improvements in safety outcomes, setting liso-cel apart from other currently available CAR-T therapies.

In conclusion, liso-cel presents several key advantages over axi-cel as a 2L treatment option for patients with early relapsed/primary refractory LBCL. Considering these factors, liso-cel represents a promising 2L treatment option that would provide a potentially more cost-effective CAR-T for a greater number of patients.

Limitations

A key limitation of the analysis is that UK clinical practice for early relapsed/primary refractory LBCL has evolved substantially since the conduct of the TRANSFORM trial, most notably with the introduction of novel bispecific antibodies, such as epcoritamab, glofitamab and the antibody drug conjugate loncastuximab tesirine as 3L+ treatment options. This is anticipated to primarily impact subsequent treatments following liso-cel, where patients predominantly received chemotherapy regimens in the TRANSFORM trial. In current UK clinical practice, the majority of these patients would be expected to receive much more effective treatment options, although there is no plausible methodology to adjust the OS data from the TRANSFORM trial to reflect the increased number of patients that would be expected to be cured in the 3L+ setting after requiring a subsequent treatment to liso-cel (Section B.3.13).

Additionally, another limitation of the economic analysis is that, as the follow-up of the TRANSFORM trial is shorter than the model time horizon, long-term extrapolation of EFS, TTNT and OS data from the TRANSFORM trial is required, which is inevitably associated with uncertainty. However, this uncertainty was mitigated by the fact that the survival data obtained from the final DCO (October 2023) of TRANSFORM were relatively mature. The median follow-up was 33.9 months, a clear plateau was observed in the KM curves for EFS and OS in both the liso-cel and SOC arms and a considerable proportion of the OS events (in the context of a curative indication) had occurred in the liso-cel and SOC arms ([redacted]% and [redacted]%, respectively). The majority of patients remaining alive after this time are likely to be cured, meaning that additional follow-up is unlikely to provide meaningful evidence that would reduce the uncertainty associated with the long-term extrapolations used in the base case economic analysis. Furthermore, the selection of the most appropriate curves was based on the recommendations outlined in NICE DSU TSD 14 and 21, based on a combination of goodness-of-fit statistics, inspection of visual fit (internal validity) as well as feedback received from clinical experts on the relative clinical plausibility of each curve (external validity). Uncertainty surrounding the long-term survival estimates of liso-cel were explored in several scenario analysis, which demonstrated the results were robust to alternative scenarios. Of particular relevance, Scenario 13, which attempted to adjust for the overestimation of SOC OS and the underestimation of liso-cel OS in the TRANSFORM trial, clearly demonstrates the potential for the base case economic analysis to be a conservative reflection of the true cost-effectiveness of liso-cel.

Conclusions

A critical unmet need exists for CAR-T cell therapy to be made available to patients with early relapsed/primary refractory LBCL as early as possible in the treatment pathway, to avoid patients needing to undergo the gruelling physical and psychological burden associated with current SOC. SOC is ultimately futile for most patients and while some patients are subsequently able to go onto receive 3L+ treatment with CAR-T cell therapy in current clinical practice, the burden associated with SOC and delays to receiving effective treatment means that some patients will die before ever being able to access CAR-T cell therapy. The introduction of liso-cel would alleviate this burden on patients, allowing them to derive benefit from CAR-T cell therapy as early as possible following failure of 1L treatment regimens, and maximising the proportion of patients who are able to be cured from their disease.

The probabilistic base case results suggest that liso-cel could increase LYG by 1.50 and QALY by [redacted] compared to SOC, and resulting in an additional [redacted] of patients still being alive at 10 years. These improvements in health benefits would be highly cost-effective for the NHS, with the base case ICERs demonstrating liso-cel is cost-effective at a WTP threshold of £20,000 per QALY, with liso-cel found to be dominant versus SOC in all base case and scenario analyses considered.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID3887_Liso-cel in LBCL_SIP_FINAL_14 May24_NoCON	FINAL	No	14th May 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (Tai PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Lisocabtagene maraleucel (shortened to 'liso-cel' within this submission)

Brand name: Breyanzi®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

Population: Liso-cel is being appraised by NICE as a new treatment for adults with **large B-cell lymphoma**[a] (LBCL) who are suitable for a **stem cell transplant** (SCT).

LBCL is a type of blood cancer. There are four key subtypes of LBCL that are considered within this submission. These are listed below and discussed further in **Section 2a**) The condition – clinical presentation and impact:

- Diffuse large B-cell lymphoma (DLBCL). This is the most common type of LBCL, accounting for around 90% of all LBCL cases in the UK[1]
- High-grade B-cell lymphoma (HGBCL)
- Primary mediastinal B-cell lymphoma (PMBCL)
- Follicular lymphoma Grade 3B (FL3B)

Specifically, liso-cel will be used as a **second-line treatment** in patients with any of the above types of LBCL that has not responded to initial treatment (known as **primary refractory disease**) or has returned within 12 months following initial treatment (known as **early relapsed disease**).

[a]Further explanations for phrases in **bold** are provided in the glossary (Section 4b) Glossary of terms). Cross-references to other sections or documents are highlighted in orange.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare products Regulatory Agency (MHRA) is reviewing whether liso-cel should be approved and granted **marketing authorisation** as a treatment for adults with primary refractory/early relapsed LBCL who are eligible for SCT. Liso-cel has been approved and granted marketing authorisation for the treatment of adults with relapsed/ refractory DLBCL, HGBCL and FL3B after two or more lines of systemic therapy.[2] The marketing authorisation extension for liso-cel to the population of interest in this appraisal is therefore pending. More information on this can be found in Document B in Section B.1.1.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

BMS currently have two multi-year collaborative projects with Macmillan Cancer Support. One is evaluating the value of prehabilitation in cancer care, and the second is supporting the creation of a workforce forecasting tool.

Whilst BMS are not engaged in other collaborative projects, they have provided grant funding to the following patient organisations over the past year: Blood Cancer UK, Cancer, Leukaemia Care, Leukaemia UK, Lymphoma Action, Maggie's Centres, Myeloma UK and Tenovus Cancer Care.

BMS have also contributed to Blood Cancer UK's 'Blood Cancer Action Plan', and have funded their 'Reducing inequality in clinical trials recruitment' project which began in April 2024.

Finally, BMS have also been a stakeholder in Tenovus Cancer Care's Lung Health Check project in Wales.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is large B cell lymphoma (LBCL)?

LBCL is a type of **non-Hodgkin lymphoma** (NHL). NHL is a term used to describe cancers of the **immune system,** the system of cells, tissues, organs that help the body fight infections and other diseases, and the **lymphatic system**, the system of tubes and glands (called **lymph nodes**) that filter body fluid and help to fight infection.

LBCL develops when **white blood cells**, called **lymphocytes**, grow out of control. There are two types of lymphocytes: **T lymphocytes (T-cells)** and **B lymphocytes** (**B-cells**). LBCL develops when the body makes abnormal B lymphocytes, so it is called a B-cell lymphoma. These abnormal B-cells grow out of control and usually build up in lymph nodes, but can build up anywhere within the body.

There are several types of LBCL that are categorised based on the type of B-cell that has become abnormal, how quickly the number of abnormal B-cells is growing, and the type of **proteins** that the abnormal B-cells are expressing. The four subtypes of LBCL considered in this submission are:

- Diffuse large B cell lymphoma (DLBCL). This is the most common type of LBCL, accounting for around 90% of all LBCL cases in the UK[1]
- High-grade B cell lymphoma (HGBCL)
- Primary mediastinal B cell lymphoma (PMBCL)
- Follicular lymphoma Grade 3B (FL3B)

These subtypes have been grouped together because the disease characteristics and treatment pathways of each of these LBCL subtypes are similar, particularly for patients with primary refractory/early relapsed LBCL**.** For simplicity and brevity, these four subtypes are referred to together as LBCL hereafter.[3] It should be noted that other LBCL subtypes do exist but are not being considered here.

How many people get LBCL?

In the UK, there are approximately 5,440 new cases of LBCL diagnosed each year.[4, 5] DLBCL is the most common subtype of NHL, representing 40% (4 in every 10) of NHL cases and 90% (9 in every 10) of all LBCL cases.[6]

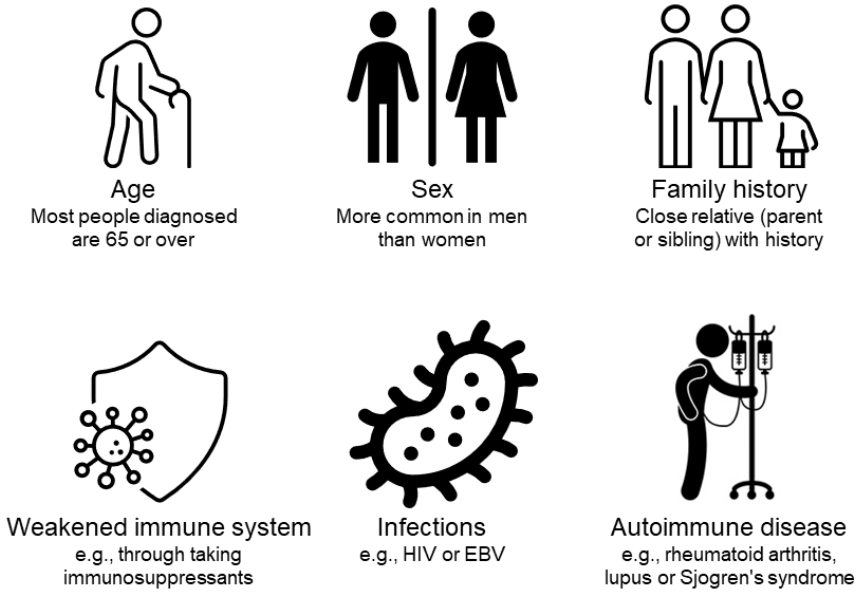
What are the key risk factors for LBCL?

The exact causes of LBCL are unknown but there are some factors that may increase the risk of developing LBCL. These factors are known as **risk factors** (see **Figure 1**).[7, 8]

The risk factors for LBCL can be categorised into those that you cannot change (non-modifiable) and those that you may be able to change (modifiable).[9] Non-modifiable risk factors include being older, being male, inheriting certain genes that make you more susceptible to developing the disease and your family history, your race or ethnic background, and some viral infections like human immunodeficiency virus (HIV). Patients with certain **immune system** diseases, such as lupus or rheumatoid arthritis, also have an increased risk of developing LBCL.[10-13]

Modifiable risk factors for LBCL include exposure to certain chemicals for long periods of time such as pesticides, and being significantly overweight, especially when younger.[10, 12-14]

Figure 1: Non-modifiable risk factors for LBCL



Abbreviations: EBV: Epstein-Barr virus; LBCL: large B-cell lymphoma; HIV: human immunodeficiency virus.

What are the signs and symptoms of LBCL?

LBCL is considered an aggressive cancer and symptoms can start or get worse in just a few weeks. The most common symptom and earliest visible sign of LBCL is usually a painless swelling or mass (lump) in a lymph node, usually in the neck, armpits or groin.[15] More general symptoms, such as unexplained weight loss, night sweats and a high temperature (fever) with no obvious cause, are shown in **Figure 2**. These symptoms are sometimes referred to as **B symptoms**.[6]

Figure 2: Initial symptoms of LBCL

Swelling in lymph nodes

Unexplained weight loss

High temperature (fever)

Night sweats

Abbreviations: LBCL: large B-cell lymphoma.

Extranodal disease

LBCL can spread to areas of the body outside of the lymph nodes, such as the chest, stomach, or bowel. When this happens, it is referred to as **extranodal disease**. Symptoms of extranodal disease depend on the area affected:[7]

- If the lymphoma spreads to the chest area, symptoms may include a cough, difficulty swallowing or shortness of breath
- If the lymphoma spreads to the stomach or bowel, symptoms may include indigestion, tummy pain or weight loss

How does LBCL progress over time?

LBCL is a curable disease. Approximately 60–70% of patients (6 to 7 in every 10 patients) with LBCL are cured after their first round of treatment.[16, 17] For patients with primary refractory/early relapsed LBCL who require a second round of treatment, life expectancy and the potential for the patient to be cured is lower. Approximately 10% of patients (1 in every 10 patients) who receive a second round of treatment for LBCL are cured.[18]

What is the impact of LBCL on quality of life?

As described above, the first sign of LBCL is typically a painless swelling within a lymph node in the neck, armpit, or groin. Patients may also have more general symptoms, including night sweats which may require a change of nightwear and bed covers, a high temperature (fever) with no obvious cause, and unexplained weight loss.[7]

Current options for patients having second-line treatment for LBCL can include undergoing an SCT (see Section 2c) Current treatment options:. Patients undergoing an SCT experience both short-term and long-term **side effects**. These can include infections, heart or lung issues, anaemia, and even the development of new cancers due to **bone marrow** DNA damage from **high-dose chemotherapy** (HDCT) before the SCT. The development of new cancers can affect about 10% of patients with LBCL treated with an SCT and can be life-threatening.[19]

Patients with LBCL often find that their day-to-day wellbeing is affected more than most other patients. This can be because of how the disease makes them feel physically, the stress of knowing that they have cancer, and the negative side effects that treatments can have on both their body and mind.[20, 21] LBCL can cause physical symptoms like **fatigue**, pain and difficulty breathing, while treatments for LBCL can lead to side effects such as nausea, hair loss and increased risk of infections. Coping with the emotional toll of a cancer **diagnosis** and undergoing treatment can be challenging for both patients and their caregivers.

Patients with primary refractory/early relapsed LBCL face additional challenges. These patients have already endured months of immunotherapy and/or chemotherapy, often with **steroids**. Steroid treatments can cause various side effects like tiredness, nausea, vomiting, diarrhoea, nerve problems, hair loss, mouth sores, and trouble sleeping. All of these aspects can have a debilitating effect on the quality of life of patients with LBCL and their caregivers.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Grading and staging

Blood cancers such as lymphomas are typically categorised as either low-grade or high-grade:

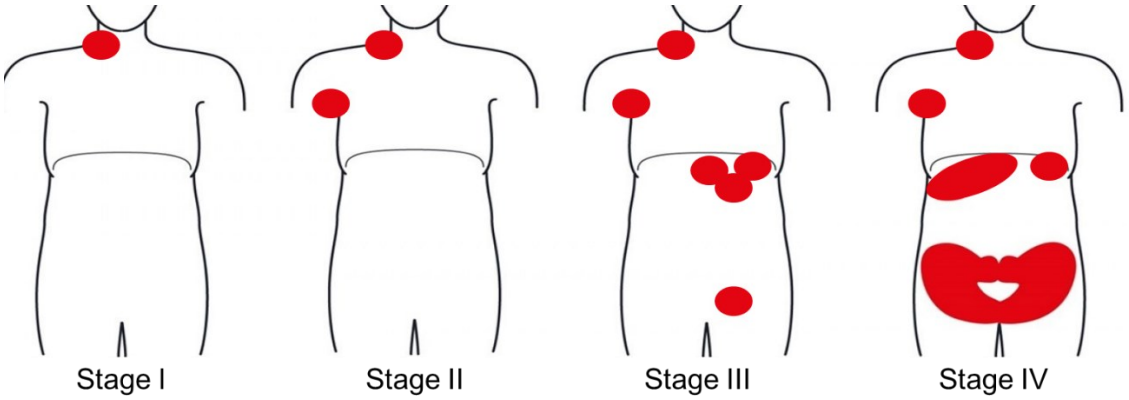
- Low-grade lymphomas are usually slow-growing
- High-grade lymphomas usually fast-growing

LBCL is a high-grade (fast-growing) lymphoma.[7]

The cancer **stage** is determined by how many lymph nodes are involved. The more lymph nodes are involved, the higher the stage (see **Figure 3**):[22, 23]

- Stage I: one lymph node or a group of close-by nodes
- Stage II: two or more lymph nodes on the same side of the **diaphragm**
- Stage III: lymph nodes on both sides of the diaphragm
- Stage IV: one or more extranodal organs or tissues (**advanced cancer**)

Figure 3: Lymphoma staging system



How is LBCL diagnosed?[24]

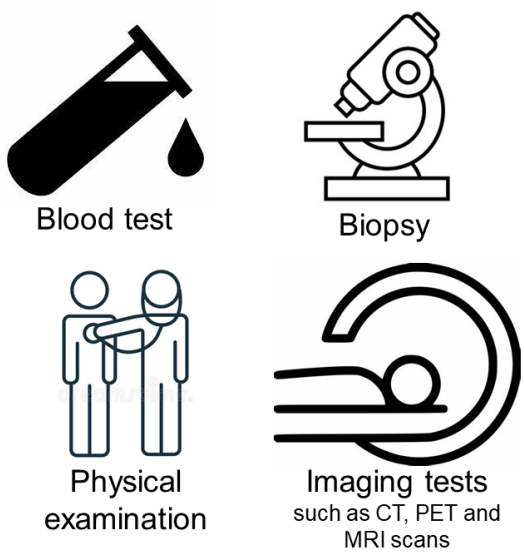
More than a third (36%) of all new NHL cases in the UK are diagnosed in people aged 75 and over and it is more common in men than women.[25] Approximately 60–70% of patients (6–7 in every 10 patients) who are diagnosed with LBCL have advanced stage disease (stage IV) at diagnosis.[26]

Diagnosing LBCL involves several steps (see **Figure 4**)**.** First, there is a physical examination where doctors will check for any enlarged lymph nodes, check the liver and **spleen** to see if they are larger than they should be and screen for B symptoms, such as fevers, night sweats, and unexpected weight loss. There will also be some imaging tests which may include a computerised tomography (CT) scan, a magnetic resonance imaging (MRI) or a positron emission tomography (PET) scan. Finally, they will also run some blood tests which include tests for viruses such as Hepatitis, HIV and EBV.

If a doctor suspects that a patient may have lymphoma they will usually perform a **biopsy**. This is where a sample of tissue is taken from the affected area and sent to a laboratory for testing. The most common place to take a tissue biopsy from is an enlarged lymph node. Patients may need to have all, or part of the lymph node removed for the biopsy. Patients may also need to have tissue biopsies taken from other areas of their body.[7]

Within the laboratory, the tissue taken during the biopsy is analysed. They will look at the shape of the cells within the tissue and use certain staining techniques to see what genetic markers the cells have. The combination of genetic markers seen in the tissue will then indicate the presence or absence of LBCL.

Figure 4: Diagnostic tests for LBCL



Abbreviations: CT: computerised tomography; MRI: magnetic resonance imaging; PET: positron emission.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for LBCL?

First-line treatment: immunochemotherapy

When treating LBCL for the first time, the main goal is to cure the disease. **First-line** treatment typically involves **immunochemotherapy**. This combines a **targeted immunotherapy** treatment called rituximab with chemotherapy and a steroid.

One of the most common immunochemotherapy regimens is called R-CHOP.[3] R-CHOP stands for:

- Rituximab: This is a targeted immunotherapy that belongs to a group of medicines called **monoclonal antibodies**. It helps to identify and attack cancer cells specifically
- Cyclophosphamide: This is a type of chemotherapy
- Doxorubicin hydrochloride: This is another chemotherapy

- Vincristine: This is another chemotherapy
- Prednisolone: This is a steroid, typically taken in tablet form

Another common immunochemotherapy regimen is called Pola + R-CHP.[7] Pola + R-CHP stands for:

- Polatuzumab vedotin: This is an **antibody-drug conjugate**
- Rituximab
- Cyclophosphamide
- Doxorubicin hydrochloride
- Prednisolone

These treatments work together to target and kill cancer cells in different ways. Patients with LBCL will usually have three **cycles** of R-CHOP or six cycles of Pola + R-CHP over a period of a few months.[7]

A cycle refers to a period of receiving treatment followed by a rest period with no treatment. The number of cycles that a patient must have and what they involve usually depends on the type of cancer and the treatments being received.

What is immunochemotherapy?

Immunochemotherapy is a type of treatment that uses the body's immune system to fight the cancer. The immune system is capable of recognising and attacking abnormal cells, including cancer cells. However, cancer cells can sometimes evade detection by the immune system or reduce the ability of the immune system to function.

Immunochemotherapy works by either stimulating the immune system to enhance its natural defences against the cancer, or by introducing man-made immune system proteins to help target cancer cells more effectively.

Immunotherapy is often given by an **intravenous drip** or injection directly into a vein, which requires patients to come to hospital for treatment and return home afterwards.

What is chemotherapy?

Chemotherapy refers to a type of treatment that uses powerful chemicals to target and kill fast-growing cells in the body. Chemotherapy is often used to treat cancer, since cancer cells grow and multiply much more quickly than most normal cells within the body. However, some normal cells in the body that also multiply quickly (such as hair and skin cells) are also affected by chemotherapy. Therefore, these treatments often lead to patients experiencing a number of side effects.

Chemotherapy can be given in two different ways:

- By an intravenous drip or injection directly into a vein
- As tablets, sometimes as a short course of treatment, or sometimes as a long-term course of treatment

What is a steroid?

Steroids are treatments that are often given with chemotherapy to treat lymphomas. They help make chemotherapy more effective. They are usually taken as tablets.

Second-line treatment: reinduction therapy, high dose chemotherapy (HDCT) and autologous stem cell transplant (SCT)

If a patient's LBCL does not respond to first-line treatment (primary refractory) or returns, a second-line treatment will be given. Patients who are fit enough to **tolerate** an SCT will first receive a different immunochemotherapy regimen, containing platinum-based chemotherapy, to try and control the cancer again. This is referred to as reinduction therapy.

Typical reinduction therapy regimens prescribed in the UK include:

- **R-GDP**, which stands for:
    - Rituximab
    - Gemcitabine: This is a type of chemotherapy
    - Dexamethasone: This is a steroid
    - Cisplatin: This is another type of chemotherapy that contains platinum
- **R-DHAP**, which stands for:
    - Rituximab
    - Dexamethasone (a steroid)
    - Cytarabine
    - Cisplatin
- **R-ICE**, which stands for:
    - Rituximab
    - Ifosfamide: This is another type of chemotherapy
    - Carboplatin: This is another type of chemotherapy that contains platinum
    - Etoposide: This is another type of chemotherapy

If this reinduction therapy works and the cancer responds, the patient will undergo a short course of HDCT followed by an SCT. HDCT involves giving much higher doses of chemotherapy drugs than usual. Typically, the HDCT regimen given to patients with LBCL in the UK is called **BEAM**.

BEAM stands for:

- Carmustine: A type of chemotherapy
- Etoposide
- Cytarabine

- Melphalan: This is another type of chemotherapy

Prior to receiving HDCT with BEAM, a patient's healthy stem cells are collected from the blood and stored so they can be put back into the body after the HDCT is complete. This is because the strength of HDCT means that in addition to killing cancer cells, it can also kill **stem cells** within the bone marrow. The type of SCT received is an **autologous stem cell transplant** (ASCT). More details of this process are provided below.

What is reinduction therapy?

Reinduction therapy refers to the immunochemotherapy regimens used after a disease has not responded or has returned after first-line treatment.

What is high dose chemotherapy (HDCT)?

HDCT involves giving much higher doses of chemotherapy drugs than usual. The purpose of HDCT is to kill more cancer cells by flooding the body with much stronger doses of chemotherapy. However, the strength of HDCT means that is also kills stem cells within the bone marrow.

What is a stem cell transplant (SCT)?

The aim of an SCT is to rescue or rebuild a patient's bone marrow following HDCT. Stem cells are blood cells at the earliest stage of development. All blood cells start off as stem cells in the bone marrow.

An autologous SCT involves collecting and storing a patient's own stem cells so they can be put back into the body after treatment. This means the patient can have much higher doses than usual of chemotherapy to treat the cancer.

The stem cells are first collected via a process called **apheresis**. The patient is connected to a machine via a drip (infusion) which takes blood from one arm, removes the stem cells and returns the blood to the other arm. Next the stem cells are preserved, frozen and stored in a stem cell laboratory. After receiving HDCT, the stem cells are thawed and given back to the patient through a drip (infusion). From here the stem cells travel through the blood to the bone marrow and begin to make new blood cells, thereby rescuing the patient's bone marrow.

Third-line treatment: CAR T-cell therapy

If second-line treatment for LBCL is unsuccessful or the cancer returns, there are a number of possible **third-line treatments** available in the UK. These include immunochemotherapy, CAR-T therapy (axicabtagene-ciloleucel or 'axi-cel'), treatment with newer therapies called **bispecifics**, antibody-drug conjugates, radiation therapy, experimental therapies, and supportive care.

What is immunochemotherapy?

The immunochemotherapy regimens that can be used in third-line LBCL are similar to those used in second-line as described above.

What is CAR-T therapy?

CAR-T therapy, short for chimeric **antigen receptor** T-cell therapy, is a special kind of immunotherapy. Liso-cel is a CAR-T therapy and in this submission, it is being appraised as a second-line LBCL treatment. In the third-line, a different CAR-T therapy, called axi-cel, has been appraised and recommended for use in third-line LBCL by NICE.[27] Axi-cel has also been appraised and recommended for use in second-line LBCL but this use is on the Cancer Drugs Fund only, meaning axi-cel is available at second-line for a limited time only.[19]

How does CAR-T therapy work?

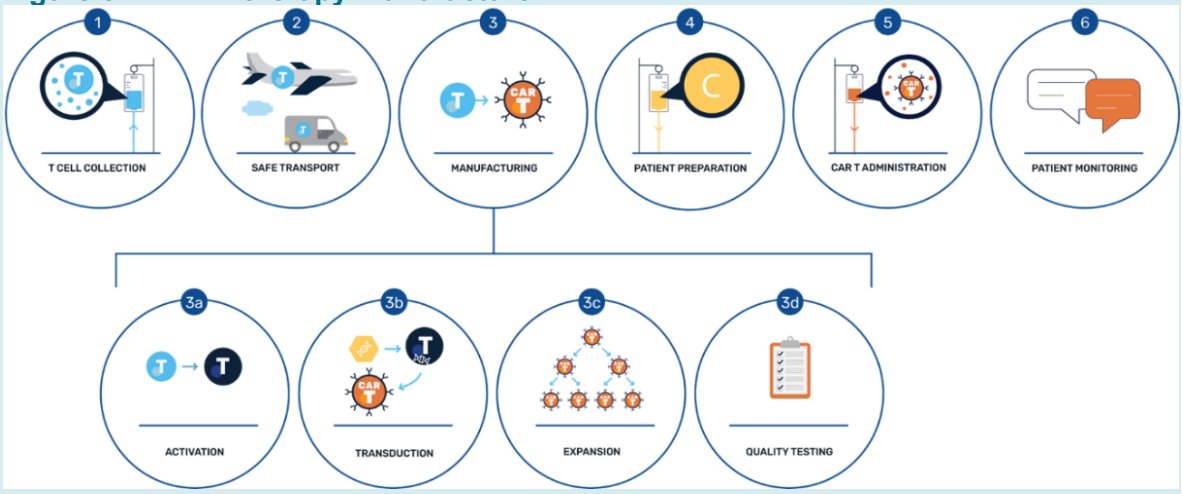
The immune system recognises foreign cells such as cancer cells in the body by identifying **antigens** (proteins) on their surface. T-cells (immune cells) have receptors (proteins) that attach to the antigens of foreign cells, which help trigger other parts of the immune system to attack the foreign cells.

The relationship between foreign cell antigens and immune cell receptors is like a lock and key. Each foreign antigen has a unique immune receptor that is able to bind to it. Cancer cells also have antigens. Without the right immune cell receptors they cannot attach to the cancer cell antigens and help destroy the cancer cells.[28]

When receiving CAR-T therapy, a patient's own T-cells are collected from their body using an apheresis machine during a process called **leukapheresis**. These cells are then flown to a laboratory in another country and reprogrammed to recognise and attack cancerous B-cells (see **Figure 5**).[28] The laboratory adds a gene for a receptor (called CAR), which helps the T-cells attach to and attack a specific cancer cell antigen (a protein on the surface of the cancer or lymphoma cell). In LBCL, the cancer cells have an antigen called CD19. To treat LBCL through CAR-T therapy, a patient's T-cells are modified to attach to the CD19 antigen.[28]

Once manufactured, the CAR T-cells are then transported back and put back inside the patient via a drip (infusion). CAR-T therapy offers an innovative, targeted approach to kill cancer cells and may provide new hope for patients with LBCL who have not been cured.

Figure 5: CAR-T therapy manufacture[28]



Abbreviations: CAR: chimeric antigen receptor

What are bispecifics?

Bispecifics are a specific type of monoclonal antibody treatment that are engineered to bind to two different antigens (the part of the target that the antibody attaches to) at the same time. Examples of bispecifics that are used in third-line LBCL in the UK include epcoritamab and glofitamab.[29, 30]

What are antibody-drug conjugates?

Antibody-drug conjugates are complex molecules composed of an antibody linked to a chemotherapy. An example of an antibody-drug conjugate that is used in third-line LBCL in the UK is loncastuximab tesirine.[31]

What is radiation therapy?

Radiation therapy or radiotherapy involves using high-energy beams of radiation to target and kill cancer cells. It is often used to treat specific areas where the cancer is located or to help relieve symptoms like pain.

What is experimental therapy?

These are treatments that are still being tested in **clinical trials** to see if they are safe and effective. Patients may have access to these treatments if they meet certain criteria and choose to participate in a trial.

What is supportive care?

Supportive care focuses on managing symptoms and improving **quality of life** for patients, especially if they are not able to undergo more aggressive treatments. It may include pain management, counselling, and other supportive services.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

LBCL from the patient perspective

Coping with LBCL can present significant challenges from the patient perspective. As part of the NICE appraisal for axi-cel in second-line LBCL (NICE TA895), a number of patient statements were provided.[19] When patients with LBCL were interviewed, the key areas of concern with regards to current treatments included insufficient response, fear or relapse, treatment side effects, and the necessity for repeated treatment cycles, which one patient described as being in a "constant confrontation with mortality".[19]

One patient who underwent SCT referred to it as the "lowest point of my life, I was completely washed out… it took two to five months to feel I was recovering". Another patient described that during her second-line chemotherapy treatment, she decided she could not continue with "chemo wrecking my body without getting rid of the cancer… it had huge impacts on my mental health".[19]

The HDCT regimen can also be particularly difficult for some patients to tolerate, with one patient reflecting on vomiting "all day long", and commenting "I was so wiped out that I could hardly stand up". Others have described treatment as "totally debilitating", causing them to experience "every unpleasant side effect imaginable. Excruciating pain, severe sickness, constipation, peripheral neuropathy, hair loss, extreme fatigue and many more".[19]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is the new treatment?

Liso-cel is a CAR-T therapy. Please see **Section 2c**) Current treatment options: for a detailed explanation of how CAR-T therapy works.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy

(3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Prior to receiving an infusion with liso-cel, patients with LBCL must undergo a number of pre-treatment phases, called leukapheresis, bridging therapy and lymphodepleting chemotherapy. These are described below in Section 3c) Administration and dosing.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Pre-treatment phases

Before undergoing infusion with liso-cel, patients with LBCL will usually undergo three pre-treatment phases (see **Figure 6**):

1. The first phase is called **leukapheresis**, where a patient's own T-cells are collected from their body using an apheresis machine. This process has been described in Section 2c) Current treatment options:.
2. Next, whilst waiting to receive their infusion of CAR-T cells, some patients will receive **bridging therapy**. Bridging therapy is usually R-GDP, which has been described in more detail in Section 2c) Current treatment options:.
3. Lastly, just before receiving the liso-cel infusion, patients will undergo a special kind of chemotherapy for three days. This chemotherapy is called **lymphodepleting chemotherapy** and is typically a combination of two chemotherapy treatments called cyclophosphamide and fludarabine. After completing three days of this lymphodepleting chemotherapy, the liso-cel infusion is administered between 2 to 7 days later.

How is liso-cel taken?

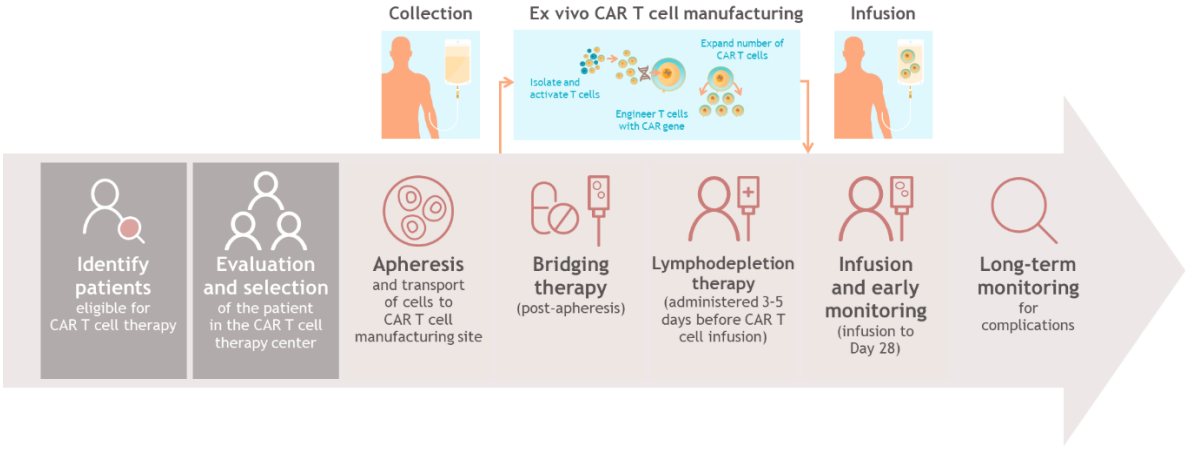
Treatment with liso-cel will be overseen by a healthcare professional who has experience in treating blood cancers and knows how to give liso-cel safely. The healthcare professional will also have training to manage any side effects that might occur.

The liso-cel infusion is administered via an intravenous drip (infusion). This usually takes 30 minutes. The doctors and nurses monitor patients closely during and after the treatment (see **Figure 6**).[32]

To help prevent any possible reactions during the liso-cel infusion, patients receiving liso-cel are given some medications before the treatment starts. These medications include paracetamol (painkiller) and diphenhydramine (antihistamine), which will be given either through a drip or tablets, about 30 to 60 minutes before the liso-cel infusion. The treatment centre will also make sure they have a medicine called tocilizumab and emergency equipment on hand in case patients need them.

Full details on the method of administration of liso-cel are provided in the Summary of Product Characteristics (see Appendix C).

Figure 6: CAR-T therapy administration and monitoring[28]



Abbreviations: CAR: chimeric antigen receptor

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Clinical trial of liso-cel in LBCL

The key **clinical trial** for liso-cel in LBCL that informs this submission is called TRANSFORM. The TRANSFORM clinical trial studied liso-cel in adults with primary refractory/early relapsed LBCL. It was a **Phase 3 clinical trial**, meaning it tested the **efficacy** and **safety** of liso-cel compared to the standard treatment, which can also be called the standard of care or SOC. The TRANSFORM trial also examined how liso-cel impacted the quality of life of the patients who received it.

In the TRANSFORM trial, patients with primary refractory/early relapsed LBCL were randomly assigned to receive one of two options:

1. Liso-cel
2. Standard of care (SOC): This was reinduction immunochemotherapy followed by HDCT and ASCT. These treatments have been described in Section 2c) **Current treatment options:**.

The TRANSFORM trial enrolled 184 adults who had either primary refractory/early relapsed LBCL after first-line immunochemotherapy and were eligible for an SCT. It was conducted in multiple locations, including USA, Europe and Japan.

More information about the TRANSFORM trial can be found here:

- A Study to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM) | ClinicalTrials.gov
- Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study | Abramson *et al.* (2023)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Clinical trial results

The TRANSFORM trial examined how well liso-cel works and how safe it is for treating patients with primary refractory/early relapsed LBCL compared to SOC. The trial measured two key outcomes:

- **Event-free survival (EFS)**: This refers to the length of time after receiving treatment for a disease that a patient does not experience any negative events related to the disease, such as a relapse or worsening of symptoms. It is a measure of how successful the treatment is in preventing these events from happening. Being event-free at 3 years means that a patient has not experienced any negative disease events for 3 years following treatment.
- **Overall survival (OS):** This refers to how long a patient lives after receiving treatment for a disease. It measures how well a treatment is able to prolong survival.

Additional outcomes that were measured in the TRANSFORM trial included:

- **Progression-free survival (PFS):** This outcome is similar to EFS, but a 'negative disease event' under PFS typically relates to disease progression.
- **Complete response rate (CRR):** Complete response rate refers to the proportion of patients who experience the disappearance of all signs of cancer in response to treatment.
- **Overall response rate (ORR):** Overall response rate refers to the proportion of patients who achieve either a complete response (the disappearance of all signs of cancer in response to treatment) or a partial response to treatment.
- **Duration of response (DoR):** Duration of response is the length of time from a patient's first relapse to disease progression or death. This represents the length of time that a cancer continues to respond to treatment without growing or spreading.

How well does liso-cel work?

In terms of EFS, the TRANSFORM trial showed that 52.6% of patients (just over half) who received liso-cel were alive and event-free 18 months after liso-cel infusion. In comparison, 20.8% of patients (one fifth) who received SOC were alive and event-free 18 months years after their treatment started.[33] This means liso-cel is more effective at preventing negative disease events than SOC.

In terms of OS, the TRANSFORM trial showed that 73.1% of patients (almost three quarters) who received liso-cel were still alive 18 months after liso-cel infusion. In comparison, 60.6% of patients (nearly two thirds) who received SOC were still alive 18 months after their treatment started.[33] This means liso-cel may have the potential to be more effective at prolonging life expectancy than SOC.

In terms of response rates, liso-cel demonstrated higher response rates in TRANSFORM compared to the SOC. This means it is more effective at shrinking tumours and reducing the spread of the disease than SOC.

The key **efficacy** results from the TRANSFORM trial are presented in Table 1. More efficacy results can be found in Document B, Section B.2.6.

Table 1: Summary of TRANSFORM key efficacy results

Key efficacy results	SOC arm (n=92)	Liso-cel arm (n=92)
EFS		
Number of patients who experienced an EFS event	71	44
% of patients alive and event-free at 12-months	22.5	57.1
% of patients alive and event-free at 18-months	20.8	52.6
OS		
Number of patients who died	38	28
% of patients alive at 12-months	72.0	83.4
% of patients alive at 18-months	60.6	73.1
PFS		
Number of patients who experienced a PFS event	52	37
% of patients alive and progression-free at 12-months	31.2	63.1
% of patients alive and progression-free at 18-months	28.8	58.2
CRR and ORR		
CRR, n (%)	40 (43)	68 (74)
ORR, n (%)	45 (49)	80 (87)
Duration of response		
Number of patients who experienced a DOR event, n/N (%)	25/45 (56)	31/80 (39)
Median DOR, months	9.1	NR

Abbreviations: CR: complete response; RR: complete response rate; DoR: duration of response; EFS: event-free survival; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; OS: overall survival; SD: stable disease; SOC: standard of care.

Source: Abramson et al. (2023).[33]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of liso-cel

Various assessment tools are used to gauge the impact of a disease and its treatment on a patient's quality of life i.e. their overall wellbeing and daily functioning. These tools often include questionnaires or surveys that cover physical, emotional, social, and functional aspects of life. Monitoring quality of life helps healthcare providers understand the holistic impact of treatment on patients and tailor interventions to improve their overall quality of life alongside managing the disease itself.

Two key quality of life questionnaires were used in the TRANSFORM trial:

1. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items (EORTC QLQ-C30)
2. The Functional Assessment of Cancer Therapy – Lymphoma subscale (FACT-Lym)

Another quality of life questionnaire also used in the TRANSFORM trial was the EuroQoL 5-Dimensions (EQ-5D) questionnaire. Results for this questionnaire are discussed in **Appendix M** and feed into the economic model described in **Section 3i**) Value and economic considerations.

EORTC QLQ-C30

The EORTC QLQ-C30 comprises 30 items, grouped into the following 15 domains: 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, nausea/vomiting, and pain), 6 single-item symptom or financial difficulty scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulty), and a global health status/quality of life scale.[34]

Patients will score themselves for each domain and these scores are then transformed to a 0 to 100 scale; a higher score represents a higher or healthier level of functioning or quality of life.

From Day 126 to Month 6 of the TRANSFORM trial, the results of the EORTC QLQ-C30 questionnaire showed that the proportion of patients with a meaningful improvement in global health status/quality of life, cognitive functioning, and fatigue was higher in the liso-cel arm than in the SOC arm. Results for the pain scores also showed a trend towards improvement in the liso-cel arm and deterioration in the SOC arm at Month 6.[34]

FACT-Lym

The FACT-LymS consists of 15 items addressing symptoms and functional limitations that are important to patients with LBCL. Items are scored on a 0 to 4 scale and combined together to a single score on a 0 to 60 scale, with a higher total score corresponding to patients experiencing fewer symptoms.[34]

The results of the FACT-LymS questionnaire showed that the proportion of patients with a meaningful improvement or deterioration in quality of life were generally similar between the liso-cel arm and the SOC arm across all clinical trial visits in the TRANSFORM trial through Month 6.[34]

In summary, the quality of life results from the TRANSFORM trial show that treatment with liso-cel did not have a detrimental effect on quality of life for patients who received it, and in many domains, patients in the liso-cel arm reported more favourable quality of life results compared with those in the SOC arm.[34]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many patients had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine can cause **side effects,** and the same medicine can produce different reactions in different patients. In clinical trials, side effects are often referred to as **adverse events** (AEs).

In the TRANSFORM trial, the overall safety profile for patients treated with liso-cel was similar to that for patients treated with SOC (see **Table 2**). As expected, there were some notable differences in terms of the AEs that are known to be specifically related to CAR-T therapy.

With AEs, the "time to onset" or "incidence rate" are typically measured. Time to onset refers to how quickly AEs occur after starting treatment, while the incidence rate indicates how often AEs happen within a specific timeframe or among a particular group of patients. These measures help healthcare providers understand the safety profile of a treatment and monitor any potential side effects that may arise during therapy.

Treatment-emergent AEs (TEAEs) are any AE observed after the initiation of study treatment and can be caused by various factors beyond the therapy itself. These may include underlying health conditions, interactions with other medications or treatments, individual patient characteristics such as age or genetic makeup, environmental factors, or even unrelated medical issues that coincide with the timing of treatment.

Table 2: TEAEs during TRANSFORM

Treatment emergent Adverse events (TEAEs)	SOC arm (n=92)	Liso-cel arm (n=92)
Patients experiencing any TEAE, n (%)	90 (99)	92 (100)
Patients experiencing any serious TEAE, n (%)	45 (49)	44 (48)
Deaths due to TEAEs, n (%)	2 (2)	2 (2)

Abbreviations: TEAE: treatment emergent adverse event: SOC: standard of care.
Source: Abramson et al. (2023).[33]

CAR-T specific AEs

CAR-T is known to be associated with specific AEs called **cytokine release syndrome** (CRS) and **neurologic toxicity** (NT).

CRS is a condition where the body's immune system releases a flood of signalling molecules called cytokines. These cytokines can cause inflammation throughout the body. It often happens as a reaction to certain treatments, like immunotherapy or certain types of medications, where the immune system is activated to fight off diseases like cancer. In severe cases, CRS can lead to symptoms ranging from mild flu-like symptoms to more serious complications like organ failure. Treatment usually involves managing symptoms and sometimes requires medications to help control the immune response.

NT refers to harmful effects on the nervous system caused by various factors such as medications, chemicals, infections, or autoimmune reactions. These toxicities can affect the brain, spinal cord, nerves, or muscles, leading to symptoms like headaches, confusion, weakness, numbness, seizures, or difficulties with movement or coordination. NT can be temporary or permanent, and treatment depends on identifying and addressing the underlying cause, which may involve medications, supportive care, or other interventions to alleviate symptoms and prevent further damage to the nervous system.

The rates of these CAR-T specific AEs experienced by patients who received liso-cel in the TRANSFORM clinical trial are presented in **Table 3**. Both AEs are graded on a scale from 1 to 5, with higher numbers indicating more serious conditions or death from the AEs.

Table 3. CAR-T specific AEs occurring after initiation of liso-cel during TRANSFORM

CAR-T specific AEs	Liso-cel arm (n=92)
Patients with CRS, n (%)	
Any grade	45 (49)
Grade 1	34 (37)
Grade 2	10 (11)
Grade 3	1 (1)
Grade 4/5	0
Time to onset, days, median (range)	5 (1–63)
Time to resolution, days, median (range)	4 (1–16)
Patients with NT, n (%)	
Any grade	10 (11)

Grade 1	4 (4)
Grade 2	2 (2)
Grade 3	4 (4)
Grade 4/5	0
Time to onset, days, median (range)	11 (7–17)
Time to resolution, days, median (range)	4.5 (1–30)

Abbreviations: AE: adverse event: CRS: cytokine release syndrome; NT: neurologic toxicities.
Source: Abramson et al. (2023).[33]

Managing side effects

In the TRANSFORM trial, patients were monitored very closely during the 10 days following liso-cel infusion, at the qualified treatment centre, for signs and symptoms of CRS or NT. Frequency of monitoring after the first week was carried out at the doctor's discretion and continued for a least 4 weeks after infusion. Patients were instructed to remain within a two-hour proximity of a qualified treatment centre for at least 4 weeks following infusion. Patients were counselled to seek immediate medical attention should signs and symptoms of CRS or NT occur at any time and treated promptly. Tocilizumab (an **immunosuppressant**) and/or a corticosteroid were used to manage CRS after infusion of liso-cel. At least one dose of tocilizumab was available per patient on site prior to infusion of liso-cel.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of liso-cel to patients with primary refractory/early relapsed LBCL are as follows:

- **Disease control:** Liso-cel demonstrated higher response rates in TRANSFORM compared to the standard of care. This means it is more effective at shrinking tumours and reducing the spread of the disease than SOC.
- **Survival advantage:** Liso-cel has shown greater potential to induce complete remissions in patients with primary relapsed or early refractory large B cell lymphoma. This means it may offer a better chance of long-term disease control or even cure compared to standard therapies.
- **Convenience and patient quality of life:** CAR-T therapy offers a one-time treatment that is less burdensome than current therapies. Patients have expressed that undergoing cycles of chemotherapy make them feel chronically unwell and serve as a reminder of their general illness, whereas the CAR-T experience involves an acute, short burst of side effects.[19]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments?

Side effects

Like all medicines, some patients may experience side effects while they are taking liso-cel. Like other CAR-T therapies, liso-cel can lead to potentially serious side effects such as CRS and NT.

As mentioned above in Section 3g) Safety of the medicine and side effects, CRS can cause flu-like symptoms, high fevers, low blood pressure, and in severe cases, organ dysfunction. NT can lead to confusion, seizures, and other neurological problems. These side effects require careful monitoring and management, which can add complexity to treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction for patient groups

The role of NICE is to assess whether a new medicine provides 'good value for money' for the NHS compared to existing medicines that are available. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to NICE using a **health economic model** (sometimes referred to as an 'economic model' or just 'the model'). The pharmaceutical company uses the **health economic model** to perform an analysis, which compares the costs and benefits of the new treatment (liso-cel) with standard of care.

How the model reflects the condition

The economic model for this submission was designed to reflect the key features of primary refractory/early relapsed LBCL in patients who are eligible for SCT and how it is treated in the UK.

The main treatment that liso-cel was compared to, referred to as the 'comparator', was SOC. This is reinduction chemotherapy followed by HDCT and SCT.

To do this, a model structure called a **partitioned survival model** was developed.

- The goal of the model was to compare the costs and quality of life of patients treated with liso-cel compared to SOC
- The model assigned patients to the two different treatments (liso-cel or SOC) and added together the costs and quality of life over the patients' lifetimes depending on which treatment they might receive in the real world
- If liso-cel maximises survival and quality of life for the amount of money it costs, liso-cel is considered a "good use of NHS resources"
- In the model, the costs of treatments patients receive after their disease progresses (i.e. treatments received in the third-line and beyond) were also included, to accurately reflect what happens in reality

Modelling how much a treatment extends life

The results of the TRANSFORM trial were used to inform the economic model. The main results from the TRANSFORM trial that were used in the model were EFS and OS. These were the main results used in the model because the length of time spent alive and without a negative disease-related event correspond to what would be considered a successful outcome when treating LBCL in clinical practice.

Given the economic model predicts survival over a patient's lifetime, results from the TRANSFORM trial were extrapolated which means they were estimated for future years beyond the end of the length of the TRANSFORM trial. Estimations of EFS and OS were included for both patients treated with liso-cel and patients treated with SOC.

Modelling how much liso-cel improves quality of life

A reduction in quality of life was modelled when a patient experiences disease progression. This reflects the fact that the mental and emotional impact of primary refractory/early relapsed LBCL would likely be increased when a patient experiences a negative disease-related event.

The quality-of-life results that informed the model were from the TRANSFORM trial, based on a questionnaire called the EQ-5D, as this was the best source of robust data and is the quality of life questionnaire typically used to inform health economic models submitted to NICE.

Modelling how the costs of current treatment differ with liso-cel

Various different costs were included in the model for both liso-cel and for SOC. These costs included:

- The cost of pre-treatment with leukapheresis, bridging therapy and lymphodepleting chemotherapy for patients receiving liso-cel
- The cost of liso-cel itself and how much it costs to administer the medicine
- The cost of standard of care medicine and how much it costs to administer these
- The cost of monitoring patients during treatment and following disease progression
- The cost of side effects that happen during treatment
- The cost of treating patients at the end of their life.

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in **Document B, Section B.3.9.2**. The main assumptions used in the model form 'the base case' which the manufacturer considers to be the most accurate and robust estimates for the different elements of the economic model.

A key assumption in the model was the estimations of long-term survival for both patients receiving liso-cel and SOC. Analyses were conducted to test the uncertainty around all model inputs. Alternative assumptions in the model were also tested and the results of these tests are explained in **Document B, Section B.3.11.3.**

Cost effectiveness results

Based on the modelling inputs and assumptions from BMS, treatment with liso-cel was associated with higher health benefits (or '**quality-adjusted life years' [QALYs]**) at a cheaper cost than standard of care. This is because in the health economic model, BMS provides liso-cel with a confidential discounted price. The results of the base case of the economic model therefore show as 'dominant'. This means that liso-cel represents 'value for money' to the NHS because it is improving the health for patients with LBCL at a cheaper cost than medicines already available.

Benefits of liso-cel not captured in the economic analysis

Treatment with liso-cel may have many different positive impacts for patients with primary refractory/early relapsed LBCL. The health economic model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example, the fact that liso-cel is a one-time only treatment. This means that patients only need to receive treatment once, and the emotional and physical burden associated with the intensive chemotherapy cycles that they would otherwise need to receive is avoided. Moreover, the psychological impact associated with a patient's disease returning, which is more likely to happen if they receive SOC, is not able to be captured within the economic analysis.

Conclusion

The benefits outlined in Section 3h) Summary of key benefits of treatment for patients and the economic analysis results above suggest that liso-cel represents good value for money and a good use of NHS resources as a new treatment for patients with primary refractory/early relapsed LBCL who are eligible for SCT.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Liso-cel is an innovative treatment which would represent an important advancement in the treatment of LBCL

LBCL is a condition that can have a significant effect on a patient's mental and emotional wellbeing and quality of life. Despite this, there are very few treatment options available that have been shown to be effective in patients with primary refractory/early relapsed LBCL. As described in this submission, the current SOC for patients with second-line LBCL involves intense immunotherapy, followed by HDCT and SCT in some patients. The HDCT is so strong that it requires patients to have a SCT to recover and restore their bone marrow. The chemotherapy can also cause uncomfortable or unpleasant side effects.

CAR-T therapy represents an entirely different approach to the treatment of LBCL and as a one-time only treatment that engineers patient's T-cells to target cancer cells, it represents a highly innovative treatment option for patients who otherwise would have to face poor outcomes with current treatment. The outcomes that can be achieved with liso-cel demonstrate that liso-cel is able to reduce the risk of patients experiencing disease progression and death compared with SOC. Unlike other CAR-T therapies, liso-cel has a highly controlled manufacturing process and ensures a specific mix of T-cells are given in every infusion, which may contribute to the favourable safety profile of liso-cel compared to other available CAR-T therapies.[35]

Currently, CAR-T therapy, like liso-cel, is only offered to these patients in the UK when they have reached their third line of treatment or later. Introducing CAR-T therapy earlier, at the second-line stage, has shown great promise in improving outcomes for patients. This earlier access could lead to better chances of curing the cancer, as patients in their second line typically have less cancer in their bodies, fewer other health problems, and are generally in better physical condition. Offering CAR-T therapy earlier could also mean that more patients get the chance to receive this innovative treatment, as some patients may not survive long enough to reach later lines of treatment, or their health may deteriorate too much for them to handle intensive therapies. Providing CAR-T therapy earlier could save more lives and offer the hope of a cure to patients with primary refractory/early relapsed LBCL.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues that are anticipated for the use of intervention in this patient population.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on LBCL:

- Diffuse large B cell lymphoma | non-Hodgkin lymphoma | Cancer Research UK
- Diffuse Large B Cell Lymphoma (DLBCL) | Macmillan Cancer Support
- Diffuse large B cell lymphoma (DLBCL) - what is it, symptoms and treatment | Blood Cancer UK
- Diffuse large B cell lymphoma | (lymphoma-action.org.uk)
- Primary mediastinal large B-cell lymphoma (PMBCL) | Macmillan Cancer Support
- Low-grade non-Hodkin lymphoma | (lymphoma-action.org.uk)

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains words or phrases highlighted in **black bold text** in this summary of information for patients. The explanation for some words or phrases might require you to read the explanation provided for other words or phrases.

Advanced cancer	The word advanced is usually used to describe cancer that has spread from where it first started to nearby tissue, lymph nodes, or other parts of the body

Antibody-drug conjugate	Antibody-drug conjugates are complex molecules composed of an antibody linked to a chemotherapy.
Antigen	An antigen is a substance that triggers the body's immune response, typically by causing the production of antibodies or activating immune cells.
Apheresis	A procedure in which blood is collected, part of the blood such as platelets or white blood cells is taken out, and the rest of the blood is returned to the patient.
Autologous stem cell transplant	A procedure in which a patient's healthy stem cells are collected from the blood or bone marrow before treatment, stored, and then given back to the patient after treatment. A stem cell transplant replaces a patient's stem cells that were destroyed by treatment with high doses of chemotherapy.
Autoimmune disease	A condition in which your immune system mistakenly attacks your body. There are lots of different types of autoimmune diseases, where the immune system attacks different parts of the body.
B cells (also called B lymphocytes)	A type of white blood cell in the immune system that helps to fight infections.
Biopsy	A biopsy is the removal of a small sample of tissue for examination, typically to diagnose or evaluate a medical condition.
Bispecifics	A type of antibody that can bind to two different antigens at the same time. Bispecific antibodies are being studied in the imaging and treatment of cancer. They are made in the laboratory.
B symptoms	A set of general symptoms that can indicate the presence of certain diseases, particularly cancers such as lymphoma. These symptoms include unexplained fever, unintentional weight loss, and excessive sweating, particularly at night, and are associated with a poorer prognosis.
Bone marrow	This is a soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made.
Bridging therapy	Therapy (usually chemotherapy) given to patients whilst they wait to receive other treatments.
Chemotherapy	A type of cancer treatment that uses drugs to kill cancer cells.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease.

Complete response	The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured. Complete response may also be referred to as complete remission.
Computerised tomography (CT) scan	A procedure that uses a computer and an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly.
Cycles	The majority of cancer treatments are given in cycles. Each cycle is often divided into a period where you receive a treatment, followed by a period of rest from treatment to allow your body to recover from any side effects. The length of each cycle and the split between the treatment and rest periods depends on the type of cancer you have, where it is in your body, if it has spread, and where it has spread to.
Cytokine release syndrome	A potentially severe immune reaction that occurs when the immune system releases a large number of cytokines (signalling proteins that help control inflammation in your body) into the bloodstream, often as a response to certain treatments, infections, or autoimmune conditions.
Diagnosis	The identification of a medical condition or disease based on the symptoms, signs, and results of medical tests and examinations.
Diaphragm	The sheet of muscle that separates your chest from your abdomen or tummy.
Early relapsed disease	The return of a disease or the signs and symptoms of a disease after a period of improvement, usually within 12 to 24 months of completion of initial treatment. In this context, early relapsed disease refers to the disease returning within 12 months.
Efficacy	The ability of a treatment to produce the desired beneficial effect on your disease or illness in a clinical trial.
Extranodal disease	This is when cancer cells spread beyond the lymph nodes to other tissues or organs in the body.
Fatigue	This is when you feel very tired, exhausted and lacking energy. It can be a symptom of the cancer or a side effect of treatment.
First-line treatment	This is the first treatment given for your disease or illness.
Health economic model	A health economic model is a model that is developed usually within Microsoft Excel. It is a simplified representation of the real world and is useful in helping to decide whether new medicines present ‘value for money’. Health economic

	models combine clinical and economic evidence from many sources that are specific to the disease being evaluated.
High-dose chemotherapy (HDCT)	The administration of cancer-killing drugs at significantly higher doses than standard chemotherapy, often utilised in the treatment of aggressive cancers, with the aim of maximising tumour cell destruction.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immunosuppressant	Medicines that prevent activity or dampen down activity of the immune system.
Immunotherapy	A type of cancer treatment that uses the body's own immune system to fight cancer.
Immunochemotherapy	Chemotherapy in combination with immunotherapy.
Intravenous drip	Some cancer treatments are diluted in a bag of fluid which is connected to a very thin tube and goes into one of your veins.
Large B-cell lymphoma (LBCL)	A cancer of the immune system or lymphatic system and the most common type of non-Hodgkin lymphoma.
Leukapheresis	A procedure that involves removal of the blood to collect specific blood cells. The remaining blood is returned to the body.
Lymph nodes (also called glands)	Small structures in the body that trap germs and abnormal cells. Found in the neck, armpit and groin. Lymph nodes are part of the immune system.
Lymphatic system	The tissues and organs that produce, store, and carry white blood cells. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells) that filter body fluid and help to fight infection.
Lymphocytes (also called B-cells/ B lymphocytes or T-cells/T lymphocytes)	Another word for white blood cells in the immune system that help to fight infections.
Lymphodepleting chemotherapy	Lymphodepleting chemotherapy refers to the administration of chemotherapy drugs aimed at reducing the number of lymphocytes in the body, typically used as a preparatory step before CAR-T therapy or other immunotherapy treatments to enhance their efficacy by suppressing the patient's immune response.

Monoclonal antibody	A type of protein that is made in the laboratory and can bind to certain targets in the body. Monoclonal antibodies are used in the treatment of many diseases, including LBCL.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
National Institute for Health and Care Excellence (NICE)	The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money.
Neurologic toxicities	Side effects that affect the nervous system, including the brain, spinal cord, or nerves.
Non-Hodgkin lymphoma (NHL)	A large group of different types of blood cancer which affect the lymphocytes (white blood cells).
Overall survival (OS)	The length of time that patients diagnosed with the disease are still alive from either the date of diagnosis or the start of treatment for a disease, such as cancer. In a clinical trial, measuring OS is one way to see how well a new treatment works.
Palliative care	A medical caregiving approach aimed at optimising quality of life and mitigating suffering among patients with serious, complex, and often terminal illnesses.
Partial response	A decrease in the size of the cancer, or the extent of cancer in the body, in response to treatment. Partial response may also be referred to as partial remission.
Partitioned survival model	A type of health economic model.
Phase 3 clinical trial	This type of clinical trial that tests the safety and how well a new treatment works (efficacy) compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
Positron emission tomography (PET) scan	A procedure in which a small amount of radioactive substance is injected into a vein, and a scanner is used to make detailed, computerised pictures of areas inside the body.
Primary refractory disease	Cancer that does not respond to first-line treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant during treatment.

Prognosis	This gives an idea about whether the cancer can be cured and what may happen in the future.
Progression-free survival (PFS)	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring PFS is one way to see how well a new treatment works. PFS may also be referred to as event-free survival or EFS.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Quality-adjusted life year (QALY)	The quality-adjusted life year (QALY) is a summary outcome measure used to estimate how well a new medicine works. It combines both quality of life and quantity of life (i.e. life expectancy). QALYs are based on quality of life data typically collected in clinical trials, which are valuations of health-related quality of life measured on a scale where full health is valued as 1 and death as 0. 1 QALY = one year spent in full health.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of wellbeing and their ability to carry out activities of daily living.
Receptors	A structure on the surface of a cell that detects stimuli.
Refractory	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.
Regulatory bodies	These are legal bodies that review the quality, safety and efficacy of medicines and medical technologies.
Relapsed	The return of a disease or the return of signs and symptoms of a disease after a period of improvement
Remission	A period of relative disease inactivity.
Response rate	The percentage of patients whose cancer shrinks or disappears after treatment.
Risk factor	Any aspect of a patient's lifestyle, environment or pre-existing health condition that may increase their risk of developing a specific disease or condition.
Safety	The number and severity of side effects.
Second-line treatment	This is the second treatment given for a disease or illness.

Side effect (also called adverse event or AE)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Spleen	An organ behind the rib cage that helps filter blood and helps fight infection.
Stage	A description of the extent of disease and where it has spread to.
Stem cell	A cell from which other types of cells develop. For example, blood cells develop from blood-forming stem cells.
Stem cell transplant	A procedure that replaces damaged or diseased stem cells with healthy ones from bone marrow or other sources. It can be used to treat conditions such as leukaemia, lymphoma, and aplastic anaemia.
Steroids	A type of medicine which reduce inflammation.
T lymphocytes (also known as T-cells)	A type of white blood cell in the immune system that identifies and fights infections and abnormalities.
Targeted therapy	Targeted cancer drugs work by 'targeting' the differences between cancer cell sand normal cells. As these therapies target cancer cells specifically, they limit damage to healthy parts of the body.
Therapy	Treatment intended and expected to alleviate a disease or disorder.
Third-line treatment	This is the third type of treatment given for your disease or illness.
Tolerate	The ability of a patient to withstand with the side effects of treatment.
Tumour	A growth of cells that multiplies in an abnormal, uncontrollable way.
White blood cells	These are cells in the body that fight disease and infection by attacking and killing germs.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Clarification questions

June 2024

File name	Version	Contains confidential information	Date
ID3887 Liso-cel EAG clarification letter	FINAL	Yes	20/06/2024

Section A: Clarification on effectiveness data

A1. Priority question: Please provide details of how 'eligibility for SCT' was defined in TRANSFORM.

The TRANSFORM trial did not include any specific definition regarding eligibility for stem cell transplant (SCT), specifically autologous stem cell transplant (ASCT), but the trial specified in its inclusion criteria that patients must be ≤75 years old, have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 and have adequate organ function (defined as per the TRANSFORM protocol).[1] Patients in the standard of care (SOC) arm were considered eligible for ASCT following a complete response (CR) or partial response (PR) to 3 cycles of SOC salvage chemotherapy (rituximab, dexamethasone, cytarabine and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP], as per physician's choice). Response was evaluated by positron emission computed tomography (PET-CT).[1]

In clinical practice, transplant eligibility for patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) is determined by a variety of factors, including age, performance status, comorbidities, presence of major organ dysfunction, and/or lack of response to salvage chemotherapy.[2-4] However, there is no clear consensus on criteria for ASCT eligibility and definitions may vary between countries, treatment centres, and clinicians.[5] Approximately 50% of patients with R/R LBCL are ineligible for ASCT (due to advanced age, poor performance status and/or organ dysfunction) and for these patients there is no established SOC and treatment is often palliative.[6-8]

In the United Kingdom (UK), the appraisal for axicabtagene ciloleucel (axi-cel) in R/R LBCL after 1L chemoimmunotherapy (TA895) highlights that 'If the disease responds, clinicians then offer high-dose chemotherapy (HDCT) and an ASCT, for those who are able to have one. Transplant suitability is based on the person's tolerance of intensive treatment and is usually only offered to people aged under 70.'[9] The patient population in the SOC arm of the TRANSFORM trial who were considered eligible for ASCT is therefore in line with the eligibility criteria for ASCT highlighted and accepted in TA895.[9]

A2. Priority question: Please confirm if all 89 people in the liso-cel arm of TRANSFORM received conforming liso-cel on an optimal timeline (i.e. did not require multiple attempts at manufacturing or harvesting). If not, please provide the details of any deviations. Please also provide this information for those on the SOC arm who received subsequent liso-cel.

There is no definition of an optimal timeline for liso-cel treatment; however, as per the TRANSFORM trial protocol, patients randomised to the liso-cel arm were to receive liso-cel infusion 29 days +/-7 days after randomisation. The median time from randomisation to liso-cel infusion was [redacted] days.[10]

Section 6.1.1 of the TRANSFORM trial protocol outlines that in the case of a technical issue during the procedure or in the processing of the product such that it cannot be used for liso-cel administration, the patient may have a second collection procedure performed.[1] Patients were to continue to meet eligibility requirements for repeat leukapheresis.[1]

Liso-cel arm

[redacted] patients randomised to the liso-cel arm and treated with liso-cel required a second leukapheresis to be performed in order to manufacture liso-cel:[10]

[redacted] Further details of these patients are provided below:

[redacted] (JUMP is the CAR-T manufacturing facility in Seatle, USA.)

SOC arm

[redacted] patients randomised to the SOC arm who subsequently crossed over and were treated with liso-cel required a second leukapheresis to be performed in order to manufacture liso-cel:[10]

[redacted] Further details of these patients are provided below:

[redacted]

A3. Priority question: Please confirm any additional processes and delays associated with the administration of non-conforming liso-cel product.

Section 7.4.6.1 of the TRANSFORM trial protocol outlines the Protocol Product Deviation Plan for liso-cel. This was a trial assessment and decision-making process, which could result in a recommendation to treat a patient with a drug product that did not meet the specification for certain non-safety related attributes (i.e. 'non-conforming' liso-cel product).[1]

In this process, the Medical Monitor and the Primary Investigator (PI) at the clinical site would need to agree that the health of the patient and the risk/benefit profile was acceptable for the patient to receive treatment. Quality Assurance then assessed the recommendation and was ultimately responsible for the drug product lot disposition. Documentation of the non-conforming drug product was submitted to local health authorities and was provided to the Investigator to submit per institutional review board/ ethics committee (IRB/EC) requirements.[1]

Section 7.4.6.2 of the TRANSFORM trial protocol outlines the Exception Use of a Non-Conforming Product.[1] Once a decision was made for the exception use of non-conforming liso-cel, country-specific requirements were followed for the release of a non-conforming liso-cel

product to treat a patient enrolled in the trial. Approval from local health authorities and/or IRBs/ECs were obtained where required. In the European Union (EU), requirements provided in Section 11.54 of the EU Guideline on good manufacturing practice specific to advanced therapy medicinal products were followed.[11] All patients needed to provide consent prior to receiving a non-conforming liso-cel product.[1]

In TRANSFORM, a total of 2 patients received a non-conforming liso-cel product. Details of these 2 patients are reported below:[12]

[redacted]The time from leukapheresis to infusion (liso-cel arm)/time from crossover approval to infusion (SOC arm) for the above 2 patients receiving a non-conforming liso-cel product was aligned with that for patients receiving a conforming product (see responses to Questions A17 and A18).[10, 12] For both patients, the receipt of a non-conforming liso-cel product was not associated with a delay in liso-cel product availability. In addition, no different safety signals were observed in these patients compared to patients who received a conforming liso-cel product.

For commercially-available liso-cel, the process in the UK is still being established. In the EU, the process for managing non-conforming liso-cel product occurrences initiates when a deviation from the Drug Product Specification is identified, triggering a laboratory investigation. Following confirmation of an out-of-specification (OOS) result and once all release criteria testing results and pertinent data are available, the Bristol Myers Squibb (BMS) Material Review Board (MRB) assesses the potential additional risks associated to the potential use of the OOS product for patients treatment upon physician's request, and alternative options.

An executive summary of the risk evaluation and the available options is provided to the treating physician upon completion of the MRB. The physician, in turn, communicates their chosen course of action for the patient via a signed physician decision form. Additional parallel submission to the national UK OOS CAR-T panel is also anticipated.

The time frame for supplying non-conforming liso-cel products can vary and is dependent on multiple factors such as the internal MRB process duration, including the quality investigation for non-conforming liso-cel, and the specific OOS attribute identified. Over the past six months, the average duration for this MRB process has been approximately seven days. The time taken by the physician to submit the physician decision form to BMS or receiving feedback from the national OOS CAR-T panel is not included in this number.

The median turnaround time in days (from apheresis to qualifying product [QP] release) for OOS liso-cel in Europe over the past 12 months, is summarised in Table 1 below.

Table 1: Median turnaround time (in days) from apheresis to QP release for OOS liso-cel in Europe

Metric	July 2023	Aug 2023	Sept 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024	April 2024	May 2024	June 2024
Liso-cel (OOS)	[redacted]											

Abbreviations: EU: European Union; OOS; out of specification; QP: qualifying product.

BMS does not require additional diagnostic, therapeutic or administrative/operational steps from the administering site other than the ones described above.

A4. Priority question: Please confirm whether you anticipate liso-cel to also be used in the third line setting for some patients, if a positive recommendation is made for this appraisal.

This submission considers the use of liso-cel in second-line (2L) LBCL for patients who are eligible for SCT and who relapsed within 12 months from completion of, or are refractory to first-line immunochemotherapy (i.e. early R/R disease) only, in line with the patient population included in the TRANSFORM trial. No third-line (3L) patients were included in the TRANSFORM trial and therefore the outcome of this appraisal will not relate to use of liso-cel in the 3L setting.[1]

A5. In the excluded studies lists (Appendix D.2.1.2) there were a number of studies excluded for insufficient/incomplete data or other reasons. These were not specified in the eligibility criteria; please provide further details of the reasons for exclusions.

Within the clinical systematic literature review (SLR) and subsequent clinical SLR updates, studies were excluded due to reasons additional to those specified in the exclusion criteria presented in the Company Submission (CS) Appendix Table 15. These additional reasons were noted as subheadings and footnotes in the excluded study lists (CS Appendix Table 18 to 23). Further details on the exclusion reasons of 'incomplete/insufficient data' or 'other' are as follows:

- 'Incomplete' or 'insufficient data': studies were excluded when any one or more of the following scenarios occurred:
    - Not enough information on prior lines of treatment (unclear line of treatment)
    - Unknown treatment line
    - Mixed treatment lines with no subgroup data
    - Mixed histologies with no subgroup data or few patients per histology of interest
    - Mixed treatment lines and histologies
- Exclusion reasons specified as 'other' included:
    - Clinical SLR:
        - February 2024 PRISMA: 2 studies were excluded for 'other' reasons. The specific reason for these exclusions was as follows: few eligible patients (n = 2)
        - March 2023 PRISMA: 14 studies were excluded for 'other' reasons. The specific reasons for these exclusions were as follows: few eligible patients (n = 13) and protocol with no result (n = 1)
        - December 2021 PRISMA: 8 studies were excluded for 'other' reasons. The specific reasons for these exclusions were as follows: few eligible patients (n = 6) and not on-topic SLR (n = 1), and correction to previously included study (n = 1).
        - June 2021 PRISMA: 13 studies were excluded for 'other' reasons. The specific reasons for these exclusions were as follows: on-topic SLR (n = 6), few eligible patients (n = 6), and not on-topic SLR (n = 1)

        - July 2020 PRISMA: 43 studies were excluded for 'other' reasons. The specific reasons for these exclusions were as follows: mixed treatment lines (n = 32) and protocol with no result (n = 11)
    - Economic SLR:
        - February 2021 PRISMA: 5 studies were excluded for 'other' reasons. The specific reasons for these exclusions were as follows: old conference abstract (n = 3), protocol with no result (n = 1), and mixed treatment line (n = 1)
    - HRQoL SLR:
        - February 2021 PRISMA, 1 study was excluded for 'other' reasons. The specific reason for this exclusion was as follows: old conference abstract (n = 1).

A6. Please provide summary details of the two included CAR-T observational studies Dahiya, 2023 and Koff, 2023 (CS Appendix Table 17).

A summary of the two included CAR-T observational studies is provided below.

Dahiya et al. (2023)

Dahiya *et al.* (2023) was a retrospective, observational, multicentre study that investigated the outcomes of patients with LBCL treated with 2L CAR-T therapy at five academic institutions in the United States of America (USA).[13]

The study included 112 patients who were leukapheresed with the intention to receive CAR-T as 2L axi-cel [n=103] and liso-cel [n=9]). All but two patients received CAR-T infusion (one manufacturing failure and one delay due to infection). Patients underwent leukapheresis between April 2022 and April 2023 and were followed-up for a median of 6.2 months. The median age was 66.5 years with a male predominance (66%), and most patients had advanced-stage disease. A significant portion (59%) had primary refractory disease.[13]

Of the 110 patients who received CAR-T therapy, 88% experienced cytokine release syndrome (CRS) and 59% had immune effector cell-associated neurotoxicity syndrome (ICANS), though no deaths were attributed to these toxicities. The overall response rate was 82.7%, with a complete remission rate of 61.8%. Progression-free survival (PFS) and overall survival (OS) at six months were 64.1% and 84.4%, respectively. The study concluded that real-world toxicities and responses were similar for axi-cel and liso-cel to those observed in the ZUMA-7 and TRANSFORM pivotal trials, respectively, despite the necessity of interim therapies and logistic delays.[13]

Koff et al. (2023)

Koff *et al.* (2023) (NCT02736357) was a retrospective, observational, multicentre study that examined the characteristics, treatment patterns, and survival outcomes of patients with R/R LBCL who received 2L therapy across various treatment eras from 2002 to 2022. Treatment eras were defined as pre-CAR-T therapy (2002–2010), CAR-T therapy available via a clinical trial (2011–2017), and post-FDA approval of CAR-T therapy (2018–2022).[14]

Data were collected from 1,523 eligible adult patients from eight US academic centres treated between 2002 and 2022, with a median follow-up of 8 months. The median age was 62 years with a male predominance (65%); high-grade LBCL subtypes comprised 16% of all cases. Autologous stem cell transplant (ASCT) and/or CAR-T therapy was planned at 2L for 989

patients (65%), of whom 463 ultimately received ASCT, 88 received CAR-T therapy, and 21 received allogeneic transplant at 2L. 494 patients were not considered for ASCT or CAR-T therapy at 2L, and 40 were unknown for ASCT/CAR-T therapy intent.[14]

Across the 1,518 analysed patients, median event-free survival (EFS) from start of 2L therapy (all types) was 4.2 months (95% confidence interval [CI]: 3.8–4.8). Median OS from start of 2L therapy (all types) was 18 months (95% CI: 17–22), and 2- and 5-year OS estimates were 46% (95% CI: 44–49%) and 35% (95% CI: 33–38%), respectively. EFS and OS improved significantly for patients initiating 2L therapy (all types) between 2011–2017 compared to 2002–2010. EFS and OS in the 2018–2022 era remained similar to 2011–2017. The results of the study showed that survival increased in treatment eras during which CAR-T therapy was available.[14]

A7. CS Appendix D.4 states in the first paragraph that 9 RCTs were included, but paragraph three states 8 unique RCTs, please clarify numbers in first paragraph of D.4.

Nine unique randomised control trials (RCTs) were identified in the clinical SLR, however only eight of these RCTs were assessed for quality, as full-text peer-reviewed publications were available for only eight of the RCTs (from 17 publications in total). The FIL-VERAL12 trial (NCT01805557) was available only as conference abstracts (Chiappella *et al.* [2019];[15] Chiappella *et al.* [2022][16]) and therefore lacked sufficient methodological data to assess study quality, so this trial was not included as part of the quality assessment.

A8. Priority question: Please confirm how patients randomised to the SOC arm of TRANSFORM were eligible for crossover. Please outline the frequency for each criterion which led to crossover occurring. Please provide a breakdown of reasons why people did not crossover?

Patients randomised to the SOC arm of TRANSFORM were eligible for crossover to liso-cel once approved by the Medical Monitor following independent review committee (IRC) confirmation of a qualifying event. A qualifying event included any of the following, as per the protocol for the TRANSFORM trial:[1]

- Failure to achieve CR or PR by 9 weeks post-randomisation (after 3 cycles of SOC)
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomisation

The IRC assesses the eligibility of patients to crossover stating whether the criteria are met or not. There is no record of the reasons why patients are not deemed eligible by the IRC.

A total of 61 patients in the SOC arm of the TRANSFORM trial were approved for crossover. The reasons for each crossover are summarised in Table 2 below. Of these 61 patients, 3 patients who were approved for crossover did not receive liso-cel or a non-conforming liso-cel product (see response to Question A9).[10, 17]

Table 2: Overview of reasons for crossover in SOC arm in TRANSFORM, crossover analysis set

	SOC arm post-crossover (N=61) n (%)
Reasons for crossover	
Progression	[redacted]
Relapse	[redacted]
Suboptimal response	[redacted]

Abbreviations: CSR: clinical study report; DCO: data cut-off; SOC: standard of care.
Source: BMS Data on File: Table 14.1.3.4 from TRANSFORM CSR: October 2023 DCO.[17, 18]

A9. CS page 53 reports that 61 patients in TRANSFORM were approved for crossover (also 61 reported in Table 11 and Appendix Figure 2) but 58 were infused with liso-cel (including one patient who received a non-conforming product). CS page 108 reports that 60 patients in the SOC arm received liso-cel as a crossover treatment, of which 57 patients received liso-cel infusion and one patient received a non-conforming product. Please clarify the numbers who were approved for crossover and the numbers who received treatment. Please also clarify why any participants approved for cross over did not receive the treatment.

BMS apologises for the oversight in the contradictory information presented within the CS here and would like to clarify that a total of 61 patients in the SOC arm of the TRANSFORM trial were approved for crossover as per the CS page 53, Table 11 and Appendix Figure 2. Of these 61 patients, 3 patients who were approved for crossover did not receive liso-cel or a non-conforming liso-cel product.[10, 17] Two of these patients approved for crossover died prior to receiving liso-cel due to disease progression and the third patient approved for crossover did not receive liso-cel due to experiencing an adverse event (AE), and subsequently died.[10]

Of the remaining 58 patients, 57 patients received liso-cel infusion and one patient received a non-conforming liso-cel product.[10, 17]

A10. Priority question: Please provide details of proportions of prior chemotherapy regimens by arm of TRANSFORM.

Details of prior chemotherapy regimens by treatment arm in the intent-to-treat (ITT) analysis set are shown in 'TRANSFORM Analysis Table 1 Summary of Prior Anti-cancer Therapies ITT Analysis Set Oct 2023 data cut-off (DCO)', which has been included in the reference pack provided alongside these responses.[19]

A11. Priority question: Please provide a table detailing the proportion of participants in TRANSFORM in each arm by each subsequent treatment.

Details of subsequent therapies by treatment arm are shown in the 'TRANSFORM Analysis Table 1 Summary of Subsequent Anti-cancer Therapies ITT Analysis Set Oct 2023 DCO', which has been included in the reference pack provided alongside these responses.[20]

In terms of subsequent chemotherapy, as an international trial, patients in the TRANSFORM trial received a wide range of chemotherapy regimens with many individual regimens being given to very small numbers of patients. Based on UK clinical opinion, in the cost-effectiveness model (CEM), the chemotherapy regimen received in 3L+ in the base case was assumed to be 100% R-bendamustine, delivered 100% in the outpatient setting.

A12. Priority question: Please provide subgroup analysis by bridging status (received bridging vs no bridging) for the outcomes in Table 4 of the TRANSFORM publication supplement (BOR, EFS, PFS and OS).

Results for subgroup analyses by bridging status for best overall response (BOR), EFS, PFS and OS are presented in Table 3 based on the final DCO (October 2023) of the TRANSFORM trial.[17]

Table 3: Subgroup analysis by bridging status in TRANSFORM, ITT analysis set

	Liso-cel arm (n=92)		SOC arm post-crossover (n=61)	
	Patients received bridging therapy (N=58)	Patients didn't receive bridging therapy (N=34)	Patients received bridging therapy (N=13)	Patients didn't receive bridging therapy (N=48)
BOR, n (%)				
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]
EFS				
Median (95% CI) EFS, Months	[redacted]	[redacted]	[redacted]	[redacted]
12-month EFS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month EFS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS				
Median (95% CI) PFS, Months	[redacted]	[redacted]	[redacted]	[redacted]
12-month PFS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month PFS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS				
Median (95% CI) OS, Months	[redacted]	[redacted]	[redacted]	[redacted]
12-month OS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

18-month OS rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOR: best overall response; CI: confidence interval; EFS: event-free survival; ITT: intention-to-treat; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; SOC: standard of care.
Source: BMS Data on File: Bridging therapy analysis from TRANSFORM CSR: October 2023 DCO.[17, 21]

A13. In TRANSFORM the SOC regimens were decided by investigators, what criteria were used to make treatment choices? Please also provide the proportions receiving R-DHAP; R-ICE; R-GDP by country.

A UK-based primary investigator (PI) for the TRANSFORM trial was asked about the choice of SOC regimens used in the trial; they deemed the choice to be very specific to the individual treating clinician and indicated that there is also no randomised evidence to suggest that one regimen is superior to another. The main factors considered when prescribing re-induction chemotherapy regimens include their own particular preference, experience using the various regimens, regional practice and most importantly low rates of toxicity, high rates of CR and regimens that are good for mobilising cells for ASCT. The UK PI indicated that all the TRANSFORM regimens met these criteria and are used in UK clinical practice.

SOC regimens as part of re-induction therapy

The proportion of patients receiving R-DHAP, R-ICE and R-GDP as part of the re-induction therapy in the SOC arm of the TRANSFORM trial, by country, are detailed below in Table 4.

Table 4: Summary of immunochemotherapy regimen (as part of re-induction therapy in the SOC arm) receipt in TRANSFORM, by country

	SOC arm (n=91) [a]		
Country	**R-DHAP (N=15) n (%)**	**R-ICE (N=58) n (%)**	**R-GDP (N=18) n (%)**
Belgium	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Sweden	[redacted]	[redacted]	[redacted]
Switzerland	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]

Footnote: [a]in the SOC arm, 91/92 patients (98.9%) were treated with re-induction therapy as one withdrew consent
Abbreviations: R-DHAP: rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, and etoposide.
Source: BMS Data on File: Summary of exposure to immunochemotherapy regimen by country from TRANSFORM CSR: October 2023 DCO.[17, 22]

SOC regimens as part of bridging therapy

The proportion of patients receiving R-DHAP, R-ICE and R-GDP as part of bridging therapy in the liso-cel arm of the TRANSFORM trial, by country, are detailed below in Table 5.

For patients in the SOC arm who crossed over and receive bridging therapy (n=13), data on immunochemotherapy were not reported per regimen but summarised overall per Anatomical Therapeutic Chemical (ATC) classification. Thus, BMS are not able to present the proportions receiving R-DHAP, R-ICE, or R-GDP as bridging therapy in the SOC arm post crossover.

Table 5: Summary of immunochemotherapy regimen (as part of bridging therapy for liso-cel) receipt in TRANSFORM, by country

	Liso-cel arm (n=58)		
Country	**R-DHAP (N=13) n (%)**	**R-ICE (N=29) n (%)**	**R-GDP (N=16) n (%)**
Belgium	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Sweden	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]

Abbreviations: R-DHAP: rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, and etoposide.
Source: BMS Data on File: Summary of exposure to bridging therapy by country from TRANSFORM CSR: October 2023 DCO.[17, 23]

A14. In TRANSFORM [redacted] received “Antineoplastic and immunomodulating agents” (CS Table 10). Please provide details of the treatments received.

Details of antineoplastic and immunomodulating agents received by treatment are shown in the ‘TRANSFORM CSR Table 14.1.9.2 Concomitant Medication Safety Analysis Set Oct 2023 DCO’, which has been included in the reference pack provided alongside these responses.[24]

A15. CS reference 45 reports that four clinical experts were on the advisory group. Please provide details of the experience of these clinicians in treating relapsed / refractory B-cell lymphomas with SOC and CAR-T therapies. Please also provide details of the region of England that these experts are from or confirm if these were all from different regions if not able to specify the region.

Information on the four clinical experts consulted as part of the advisory board, including the region in England they practice, their experience in lymphoma, and their experience treating lymphoma with SOC and CAR-T, is detailed in Table 6.

Table 6: Details of regions and experience of clinical experts

Expert	Region (England)	Lymphoma experience	SOC experience	CAR-T experience
Clinical Expert 1	North West	International lymphoma expert, PI on multiple lymphoma clinical trials including CAR-T trials. Member of the NCRI high-grade study group.	Decades	Lead for wave 1 CAR-T centre
Clinical Expert 2	Midlands	International lymphoma expert and NCCP panellist. Chair of the NCRI high grade study group	Decades	1 year
Clinical Expert 3	London	National CAR-T expert, specifically in RWE for CAR-T in the UK. Member of the NCRI high-grade study group.	Decades	Lead for wave 1 CAR-T centre
Clinical Expert 4	South	International lymphoma expert, PI on multiple clinical trials including CAR-T trials. Chair of the NCRI Lymphoma executive group and a member of the high-grade study group.	Decades	2 years

Abbreviations: CAR-T: chimeric antigen receptor T-cell; NCRI: National Cancer Research Institute; NCCP: National Cancer Control Programme; PI: primary investigator; RWE: real world evidence; SOC: standard of care; UK: United Kingdom.

A16. The EAG notes contradictory information on Grade 3/4 AESIs, reported across the text and Table 29 in section B.2.10.3. Please confirm which is correct.

BMS can confirm that the Grade 3/4 adverse events of special interest (AESIs) listed in the CS Table 29 are correct, however the text in section B.2.10.3 incorrectly attributed these values to the opposite trial arms. BMS apologises for this oversight. The text 'AESIs of Grade 3/4 occurred in [redacted] patients ([redacted]%) who received liso-cel and [redacted] patients ([redacted]%) who received SOC' should be corrected to 'AESIs of Grade 3/4 occurred in [redacted] patients ([redacted]%) who received **SOC** and [redacted] patients ([redacted]%) who received **liso-cel**.'

A17. The EAG notes the report mentions that people crossing over to liso-cel received liso-cel with a median of [redacted]. Please confirm how this was calculated as the company submission contains contradictory information on what this is based on.

BMS apologises for the oversight regarding the contradictory information on how the median of [redacted] was derived. On p.53 of the CS, the median of [redacted] was stated to correspond to the median time from discontinuation of SOC to infusion of liso-cel. However, p.64, 67 and 95 of the CS stated that this median corresponds to the median time from progression to liso-cel infusion.

BMS would like to confirm that the median of [redacted] relates to the time from crossover approval to liso-cel infusion, with further details listed in Table 7 below, based on the May 2022 DCO of the TRANSFORM trial.[10] The criteria for crossover approval has been outlined in the response to Question A8 above. Identical results are expected from the final October 2023 DCO of the

TRANSFORM trial as no further patients crossed over between May 2022 and October 2023.

Table 7: Overview of manufacturing summary in TRANSFORM, safety analysis set

Time from crossover approval to liso-cel infusion (days)	SOC arm post-crossover (N=58)[a]
n	58
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]

[a]Includes patient who received non-confirming product of liso-cel.
Abbreviations: Q1: first quartile; Q3: third quartile; SD: standard deviation; SOC: standard of care.
Source: BMS Data on File: Table 14.3.1.1.1.3.4 from TRANSFORM CSR: May 2022 DCO.[10, 25]

A18. Priority question: Please provide summary information (mean, median, min, max IQR) on the time from leukapheresis (or similar key milestone) until liso-cel infusion for the liso-cel arm of TRANSFORM.

Summary information on the time from leukapheresis, randomisation and last dose of lymphodepleting chemotherapy to liso-cel infusion for patients in the liso-cel arm are presented in Table 8 below, based on the May 2022 DCO of the TRANSFORM trial.[10] These results were not re-examined in the final October DCO of the TRANSFORM trial as all liso-cel arm patients were infused by May 2022 and therefore results would not have changed.

Table 8: Summary information of exposure to liso-cel in TRANSFORM, safety analysis set

	Liso-cel arm (N=92)
Time from leukapheresis to liso-cel infusion (days)	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Time from randomisation to liso-cel infusion (days)	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Time from last dose of LDC to liso-cel infusion (days)	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]

Q1, Q3	[redacted]
Min, Max	[redacted]

Footnote: [a][redacted]/92 patients discontinued before lymphodepleting chemotherapy
Abbreviations: LDC: lymphodepleting chemotherapy; Q1: first quartile; Q3: third quartile; SD: standard deviation.
Source: BMS Data on File: Table 14.3.1.1.1.3.4 from TRANSFORM CSR: May 2022 DCO.[10, 25]

A19. Priority question: Please provide the statistical analysis plan for TRANSFORM.

The TRANSFORM statistical analysis plan (SAP) 'TRANSFORM SAP' has been included in the reference pack provided alongside these responses.[26]

A20. Priority question: Please re-perform the EFS and PFS analyses without censoring for treatment switching.

As presented below in Table 10 as part of the response to A21, [redacted] patients were censored for EFS due to the start of a new antineoplastic therapy for reasons other than efficacy concerns. Therefore, the EFS analysis without censoring for treatment switching is equivalent to the original EFS analyses presented in Figures 6 and 22 of the CS Document B.

Results for PFS (based on IRC assessment) without censoring for treatment switching are presented in Figure 1 and Table 6 below. PFS results without censoring for treatment switching resulted in a shorter median PFS for the liso-cel arm at [redacted] months (95% CI: [redacted]) whilst it was [redacted] (95% CI: [redacted]) when censored for treatment switching (Table 17 of CS Document B). Similarly, PFS results without censoring for treatment switching resulted in a shorter median PFS in the SOC arm at [redacted] months (95% CI: [redacted]) compared to [redacted] months (95% CI: [redacted]) when censored for treatment switching (Table 17 of CS Document B).

However, liso-cel remains superior to SOC in terms of PFS without censoring for treatment switching, with a stratified hazard ratio (HR) of [redacted] (95% CI: [redacted]) and greater estimated PFS rates at all timepoints. When PFS results were censored for treatment switching, a higher stratified HR of [redacted] (95% CI: [redacted]) and higher PFS rates were observed across all timepoints for both arms (Table 17 of CS Document B).

Figure 1: Kaplan-Meier for PFS without censoring for treatment switching in TRANSFORM, ITT analysis set

Abbreviations: IRC: independent review committee; ITT: intention-to-treat; PFS: progression-free survival.
Source: BMS Data on File: PFS without censoring for treatment switching from TRANSFORM CSR: October 2023 DCO.[17, 27]

Table 9: PFS without censoring for treatment switching in TRANSFORM, ITT analysis set

	Liso-cel arm (N = 92)	SOC arm (N = 92)
Time to event - n (%)		
Number of patients with event	[redacted]	[redacted]
Death	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Start of a new antineoplastic therapy	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Time to event (months)		
25th Percentile (95% CI)[a]	[redacted]	[redacted]
Median (95% CI)[a]	[redacted]	[redacted]
75th Percentile (95% CI)[a]	[redacted]	[redacted]
PFS rate		
PFS rate at 6 months % (SE)	[redacted]	[redacted]
Two-sided 95% CI[b]	[redacted]	[redacted]
PFS rate at 12 months % (SE)	[redacted]	[redacted]
Two-sided 95% CI[b]	[redacted]	[redacted]
PFS rate at 18 months % (SE)	[redacted]	[redacted]
Two-sided 95% CI[b]	[redacted]	[redacted]
PFS rate at 24 months % (SE)	[redacted]	[redacted]
Two-sided 95% CI[b]	[redacted]	[redacted]
PFS rate at 36 months % (SE)	[redacted]	[redacted]
Two-sided 95% CI[b]	[redacted]	[redacted]
Hazard ratios		

Stratified hazard ratio (95% CI)[c] (experiment vs control)	[redacted]
Unstratified hazard ratio (95% CI)[d] (experiment vs control)	[redacted]

[a]Median, 25th, and 75th percentile estimates are from Kaplan-Meier product-limit estimates.
[b]Greenwood's formula.
[c]Based on a stratified Cox proportional hazards model.
[d]Based on an unstratified Cox proportional hazards model.
Abbreviations: CI: confidence interval; PFS: progression-free survival; SE: standard error; SOC: standard of care.
Source: BMS Data on File: PFS without censoring for treatment switching from TRANSFORM CSR: October 2023 DCO.[17, 28]

A21. Priority question: Please provide details on the number of people censored in each analysis (EFS, PFS, OS) by the reason why they were censored.

Details for censoring for EFS, PFS (based on IRC assessment) and OS have been summarised in Table 10, Table 11, and Table 12, respectively. Of note, [redacted] patients were censored for EFS due to the start of a new antineoplastic therapy for reasons other than efficacy concerns.

Table 10: Reasons for censoring for EFS in TRANSFORM, ITT analysis set

	Liso-cel arm (N=92)	SOC arm (N=92)		
		Non-crossover (N=31)	Crossover (N=61)	Total (N=92)
Number of patients censored (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored on date of randomisation	[redacted]	[redacted]	[redacted]	[redacted]
No baseline, or no post-baseline response assessment and no death	[redacted]	[redacted]	[redacted]	[redacted]
Censored on date of last tumour assessment on-study	[redacted]	[redacted]	[redacted]	[redacted]
Failure to proceed to HDCT and HSCT due to refusal or failure to collect or mobilise stem cells	[redacted]	[redacted]	[redacted]	[redacted]
Start of a new antineoplastic therapy for reasons other than efficacy concerns	[redacted]	[redacted]	[redacted]	[redacted]
No death, no progressive disease, no failure to achieve CR or PR by 9 weeks post-randomisation and no start of new antineoplastic therapy due to efficacy concerns	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; EFS: event-free survival; HDCT: high-dose chemotherapy; HSCT: haematopoietic stem cell transplant; PR: partial response; SOC: standard of care.
Source: BMS Data on File: EFS IRC reason for censoring from TRANSFORM CSR: October 2023 DCO.[17, 29]

Table 11: Reasons for censoring for PFS based on IRC in TRANSFORM, ITT analysis set

	Liso-cel arm (N=92)	SOC arm (N=92)		
		Non-crossover (N=31)	Crossover (N=61)	Total (N=92)
Number of patients censored (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored on date of randomisation	[redacted]	[redacted]	[redacted]	[redacted]
No baseline, or no post-baseline response assessment and no death	[redacted]	[redacted]	[redacted]	[redacted]
Censored on date of last tumour assessment on-study	[redacted]	[redacted]	[redacted]	[redacted]
Start of a new antineoplastic therapy before death or progressive disease	[redacted]	[redacted]	[redacted]	[redacted]
No death, no progressive disease	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IRC: independent review committee; PFS: progression-free survival; SOC: standard of care.
Source: BMS Data on File: PFS IRC reason for censoring from TRANSFORM CSR: October 2023 DCO.[17, 30]

Table 12: Reasons for censoring for OS in TRANSFORM, ITT analysis set

	Liso-cel arm (N=92)	SOC arm (N=92)		
		Non-crossover (N=31)	Crossover (N=61)	Total (N=92)
Number of patients censored (%)	[redacted]	[redacted]	[redacted]	[redacted]
Last date patient is known to be alive				
No death	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; SOC: standard of care.
Source: BMS Data on File: OS reason for censoring from TRANSFORM CSR: October 2023 DCO.[17, 31]

A22. Priority question: Please clarify the PFS censoring rule as the CS states "patients who received a new treatment were censored from the PFS analysis if this occurred before progression in TRANSFORM", but this is not explicitly described in Table 12.

BMS can confirm that the PFS censoring rule in the TRANSFORM trial included patients who received a new treatment. Further details on the censoring rules for PFS are summarised in Table 13 below. In addition to the event and censoring rules described, the following conditions were taken into account, as noted in the TRANSFORM SAP:[26]

- Both allogenic and autologous HSCT were considered as a new antineoplastic therapy
- For the SOC arm, in the case of toxicity or no satisfactory response as per investigator judgement to the selected SOC regimen, a switch within the 3 defined SOC regimens was allowed and was not considered as a new antineoplastic therapy

- Radiation therapy was considered a new antineoplastic therapy for efficacy concerns when not planned in the treatment strategy

Table 13: Event and censoring rules for PFS in TRANSFORM

Situation	Time at which patient has Event or is Censored	Situation outcome
No baseline, or no post-baseline response assessment and no death	Randomisation date	Censor
Death	Death date	Event
Progressive disease	Progressive disease date	Event
Start of a new antineoplastic therapy before death or progressive disease	Last adequate efficacy assessment date with no evidence of progressive disease	Censor
No death or no progressive disease	Last adequate assessment date with no evidence of progressive disease	Censor

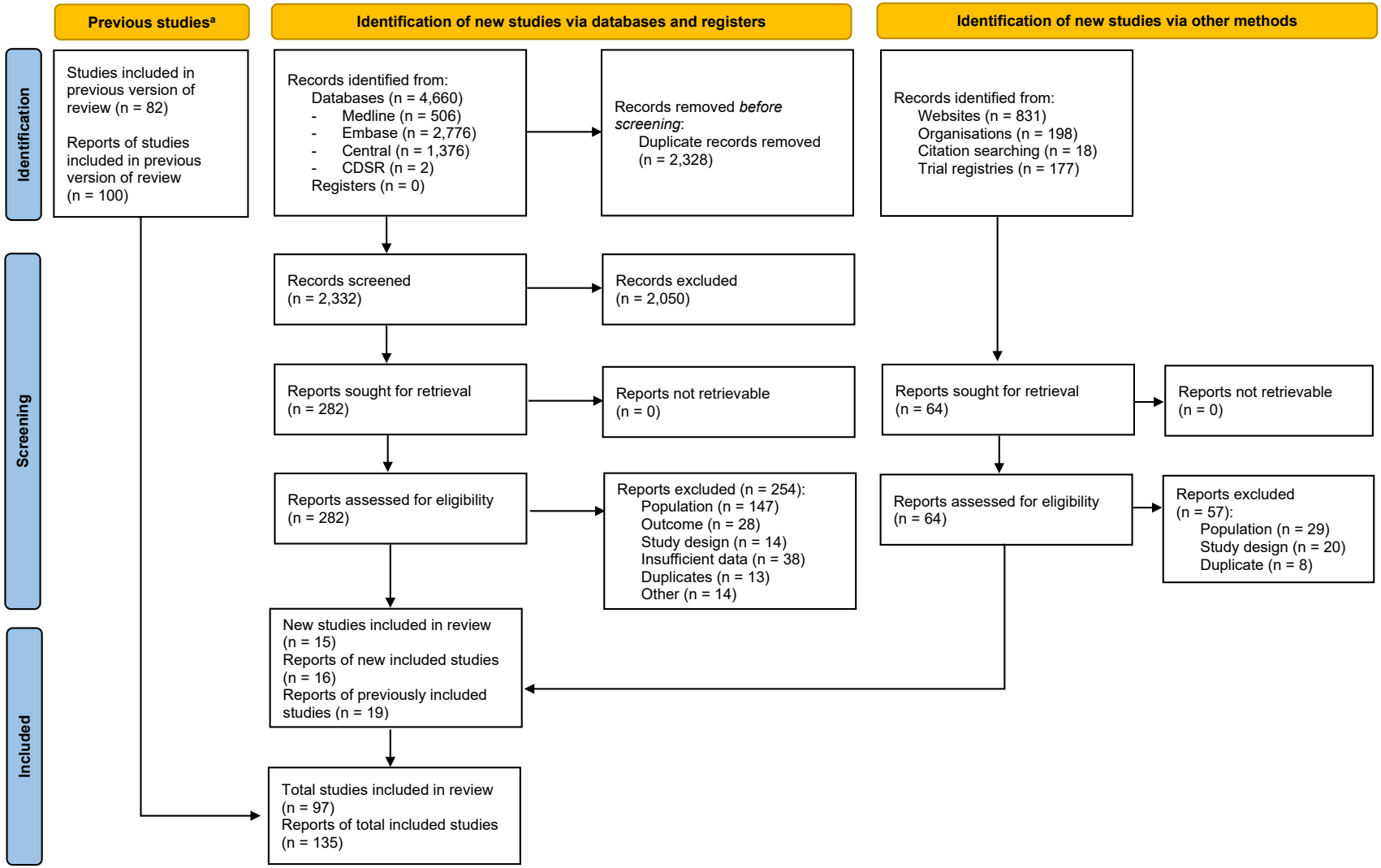
Abbreviations: PFS: progression-free survival.
Source: BMS Data on File: TRANSFORM SAP.[26]

A23. Please provide the PRISMA flow diagrams for the clinical systematic literature review searches carried out in October 2017, April 2019, July 2020, June 2021, December 2021 and March 2021.

The PRISMA flow diagrams for the previous clinical SLRs updates are presented in Figure 2 to Figure 6 as follows:

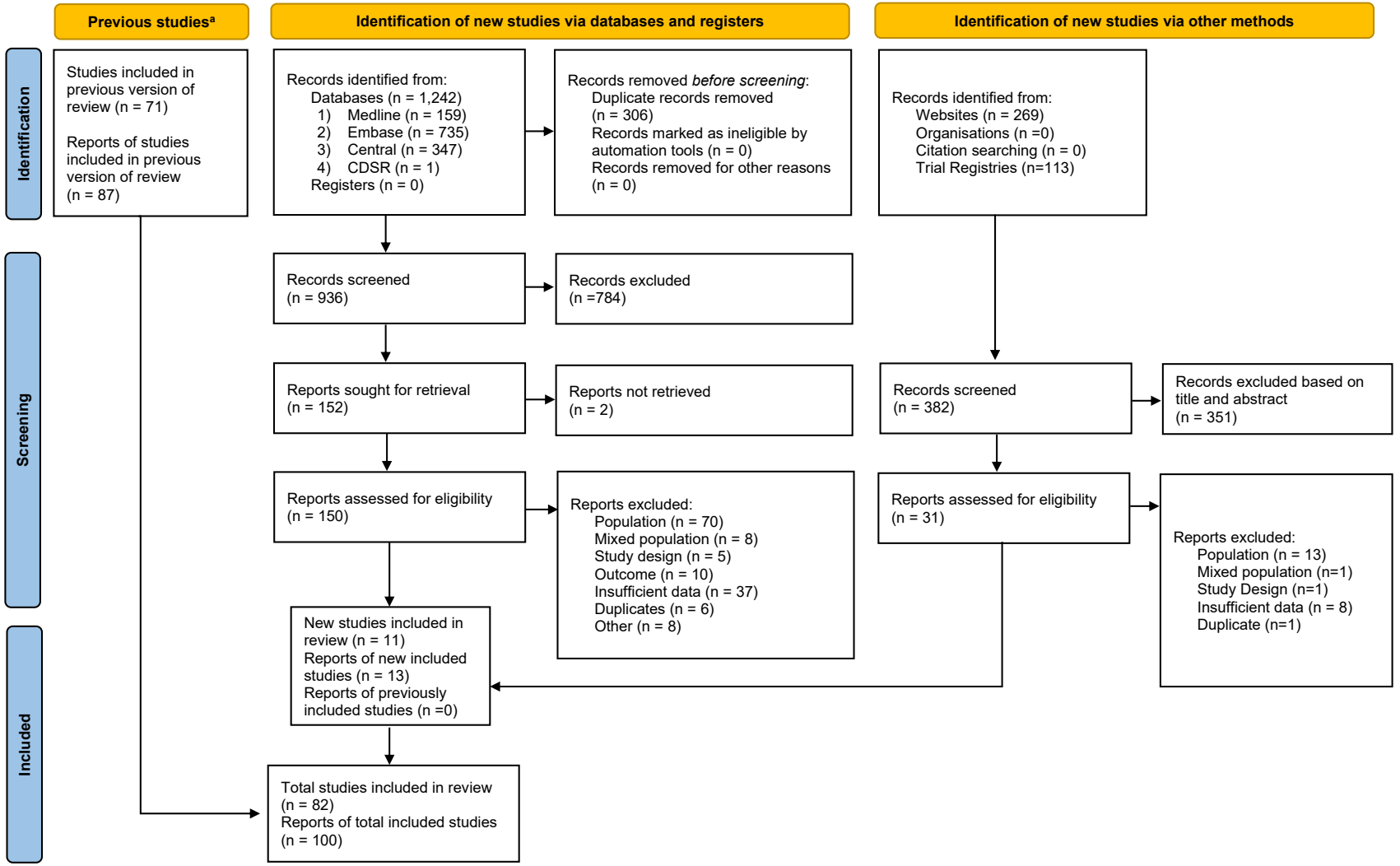
- **March 2023:** Figure 2
- **December 2021:** Figure 3
- **June 2021:** Figure 4
- **July 2020:** Figure 5
- **October 2017 (original SLR search) and April 2019 (subsequent update) combined:** Figure 6

Figure 2: PRISMA diagram for the March 2023 clinical SLR



[a] 'Previous studies' refers to the studies identified in the October 2017, April 2019, July 2020, June 2021 and December 2021 SLR updates.

Figure 3: PRISMA diagram for the December 2021 clinical SLR



[a] 'Previous studies' refers to the studies identified in the October 2017, April 2019, July 2020 and June 2021 SLR updates.

Figure 4: PRISMA diagram for the June 2021 clinical SLR

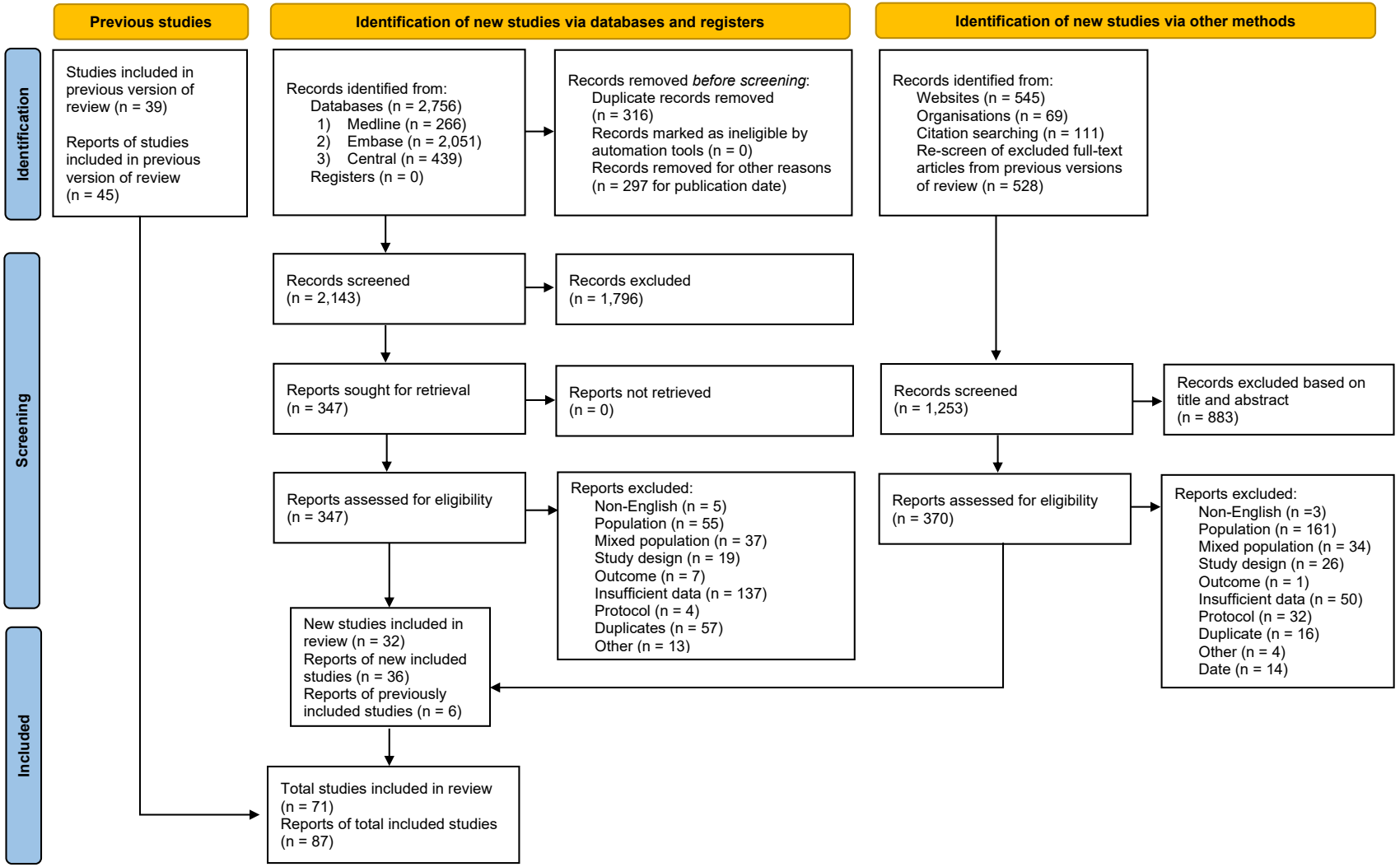


Figure 5: PRISMA diagram for the July 2020 clinical SLR

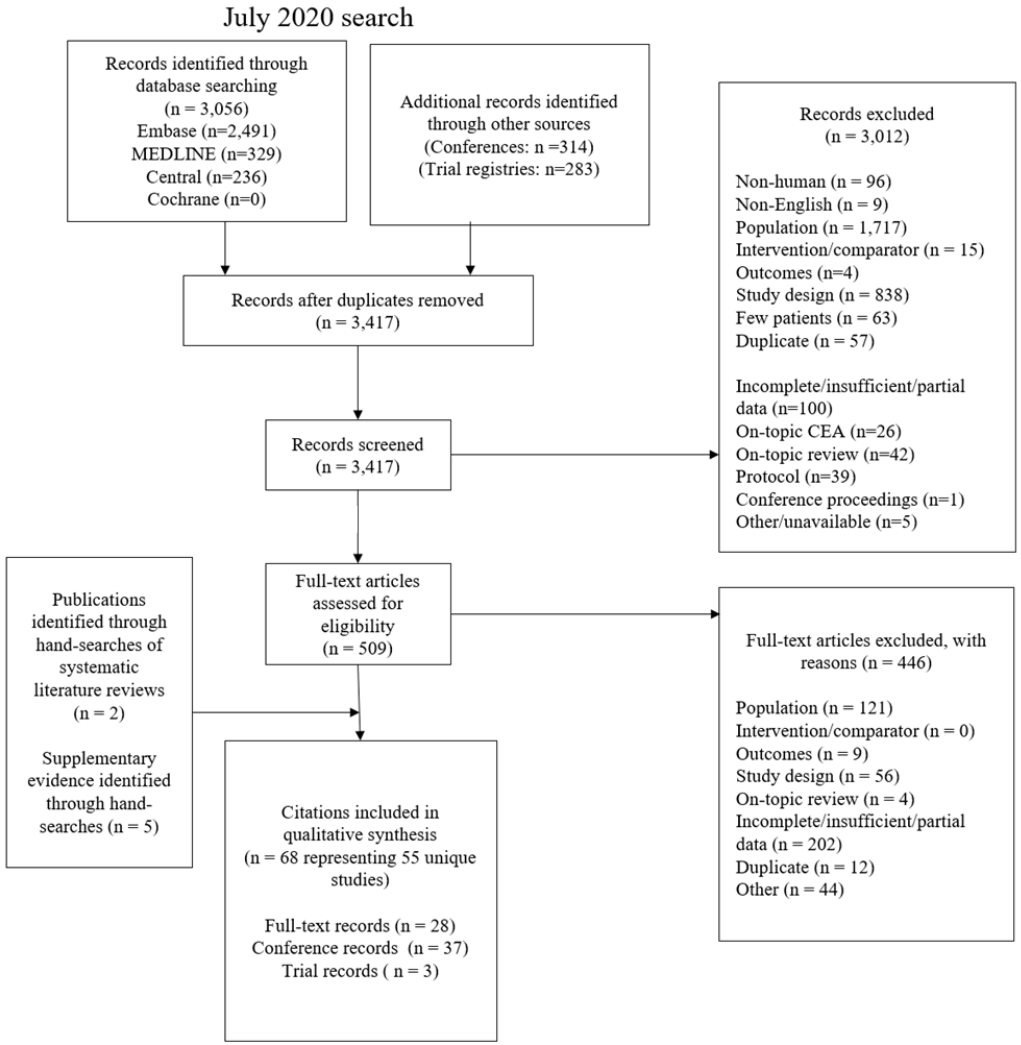
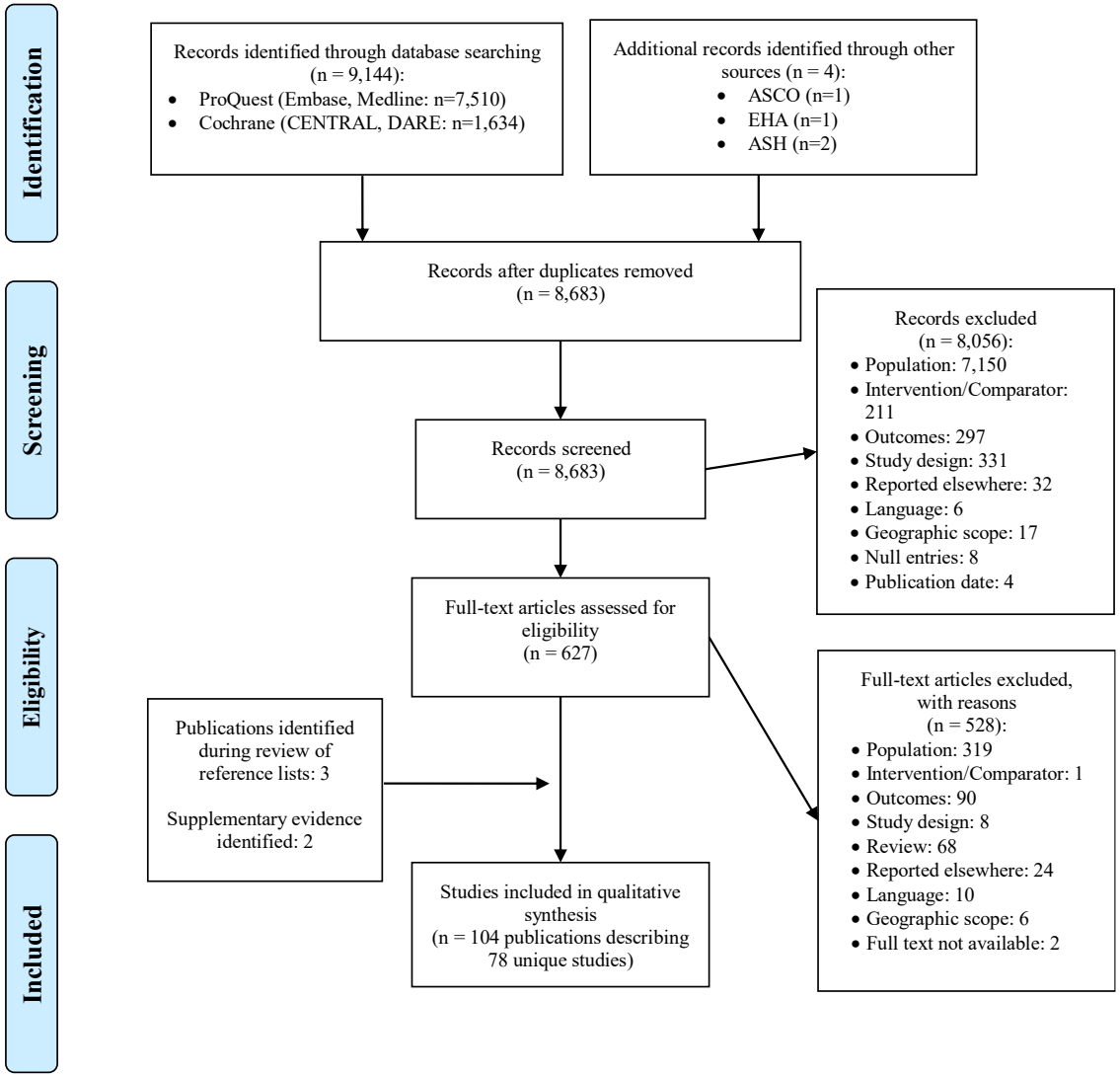


Figure 6: Combined PRISMA diagram for theOctober 2017 clinical SLR, including subsequent update in April 2019

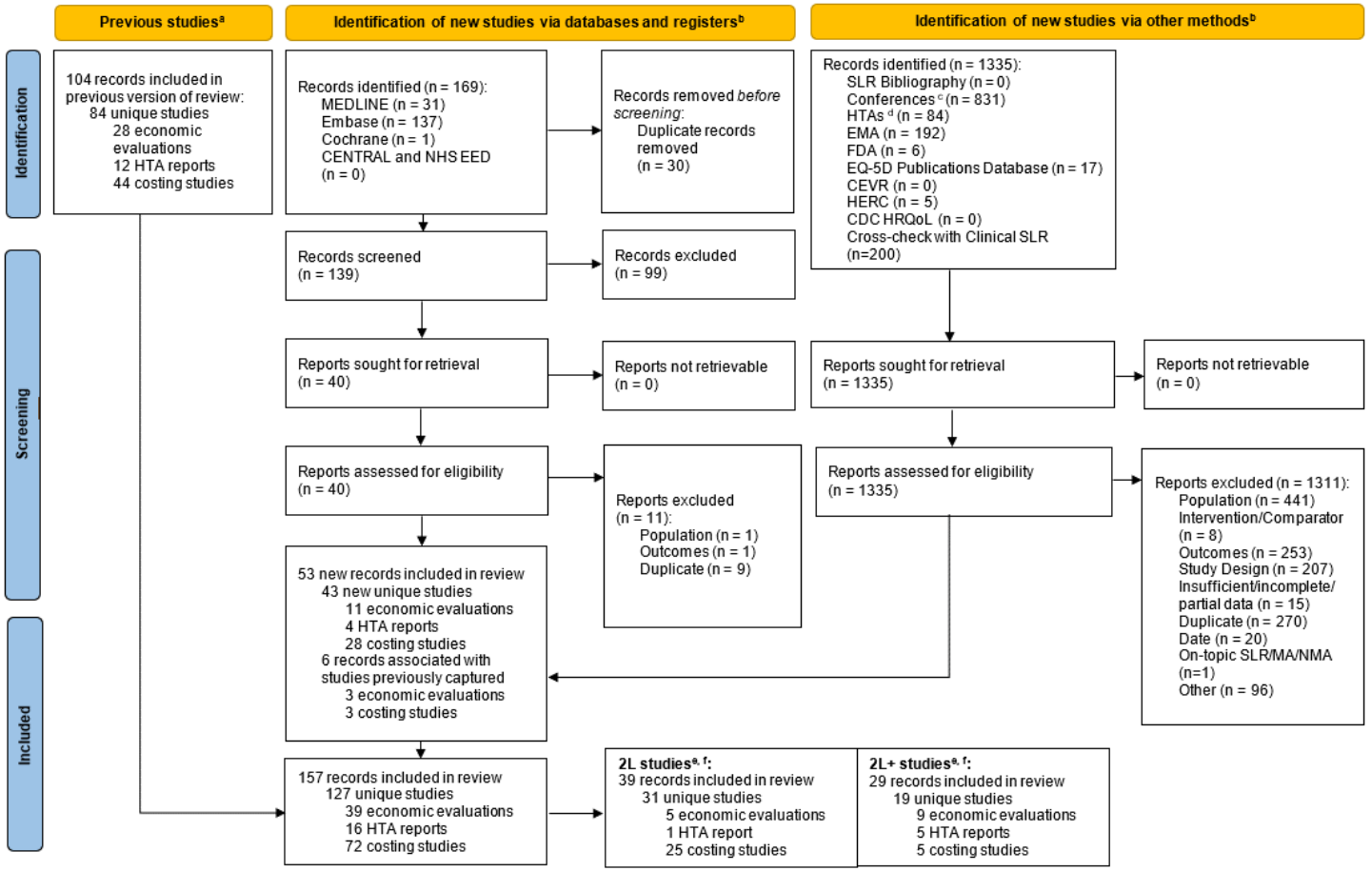


A24. Please provide the full PRISMA flow diagrams for the economic systematic literature review carried out on the 21st April 2020 and updated on the 8th June 2020, 5th February 2021, 2nd May 2022, and 1st March 2023.

The PRISMA flow diagrams for the previous economic evidence SLR updates are presented in Figure 7 to Figure 9**Error! Reference source not found.** as follows:

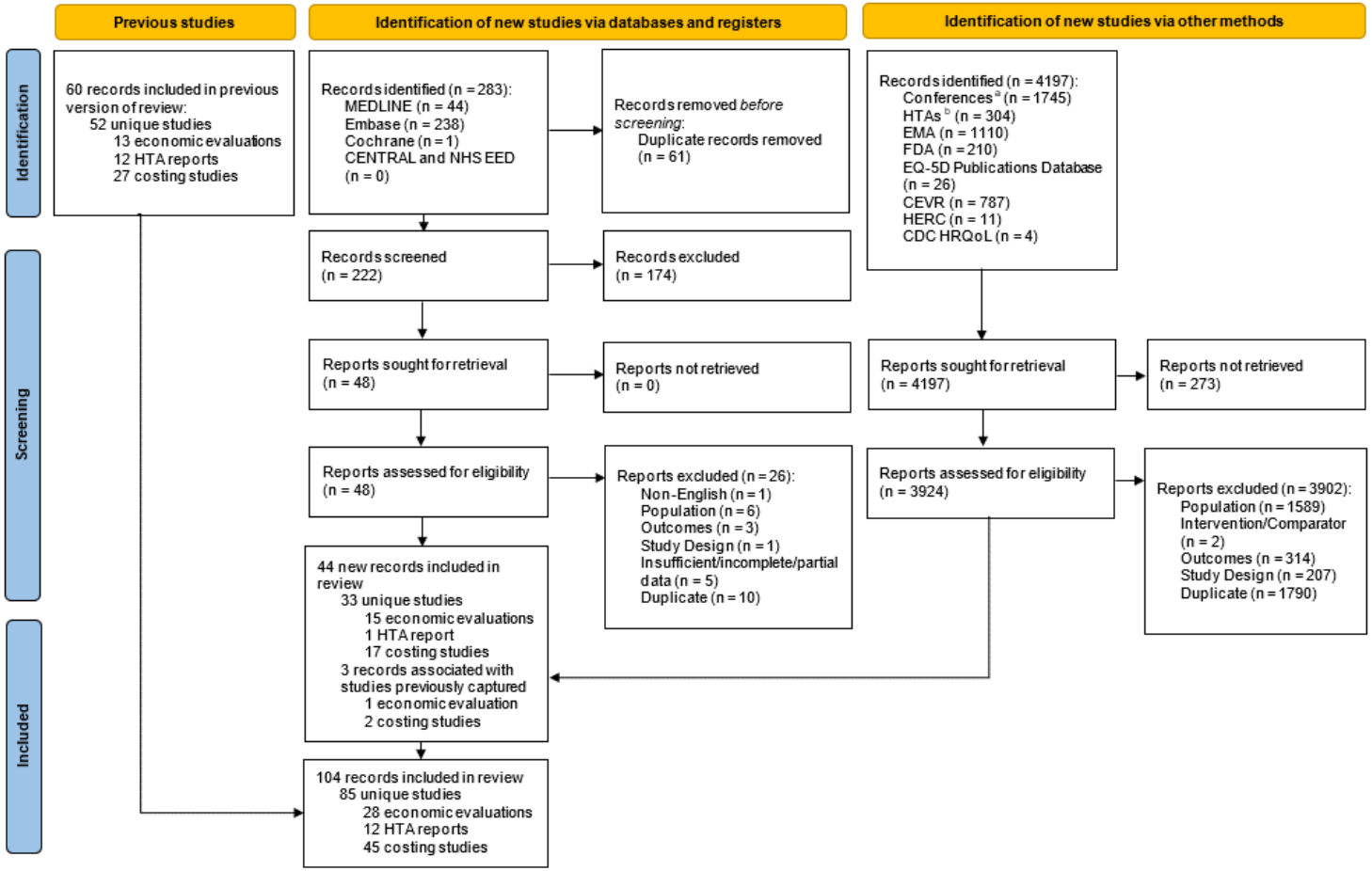
- **1st March 2023:** Figure 7
- **2nd May 2022:** Figure 8
- **21st April 2020 (original SLR search), 5th February 2021 (update) and 8th June 2020 (update) combined:** Figure 9

Figure 7: PRISMA diagram for the March 2023 economic evidence SLR



[a] 'Previous studies' refers to the studies identified in the 21st April 2020, 8th June 2020, 5th February 2021, 2nd May 2022 searches.
[b] 'Identification of new studies' refers to the present search conducted on 1st March 2023.
[c] Conferences searched included: American Association for Cancer Research (n=85), American Society of Hematology (n=691), European Organisation for Research and Treatment of Cancer (n=12), International Society of Pharmacoeconomic and Outcomes Research (n=19), International Workshop on non-Hodgkin Lymphoma (n=24).
[d] Sources of HTAs searched included: Canadian Agency for Drugs and Technologies in Health (n=27), Institut National d'Excellence en Santé et Services Sociaux (n=9), National Institute for Health and Care Excellence (n=14), Pharmaceutical Benefits Advisory Committee (n=25), and Scottish Medicines Consortium (n=9).
[e] Includes one economic evaluation and two costing studies that reported outcomes for both a 2L subgroup and an overall 2L+ population.
[f] Includes nine costing studies that also report outcomes for a 3L+ population.

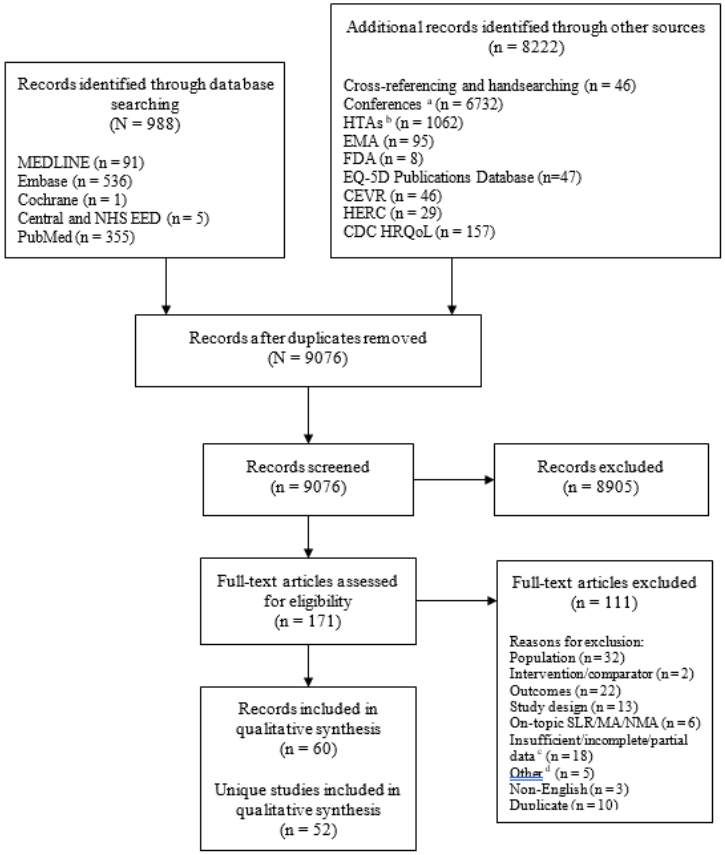
Figure 8: PRISMA diagram for the May 2022 economic evidence SLR



[a] Conferences searched included: American Association for Cancer Research (n=426), American Society of Clinical Oncology (n=313), American Society of Hematology (n=745), European Hematology Association (n=178), European Society for Medical Oncology (n=33), International Society of Pharmacoeconomic and Outcomes Research (n=50).

[b] Sources of HTAs searched included: Canadian Agency for Drugs and Technologies in Health (n=22), Institut National d'Excellence en Santé et Services Sociaux (n=64), National Institute for Health and Care Excellence (n=73), Pharmaceutical Benefits Advisory Committee (n=13), and Scottish Medicines Consortium (n=132).

Figure 9: Combined PRISMA diagram for the April 2020 economic evidence SLR, including subsequent updates conducted in June 2020 and February 2021



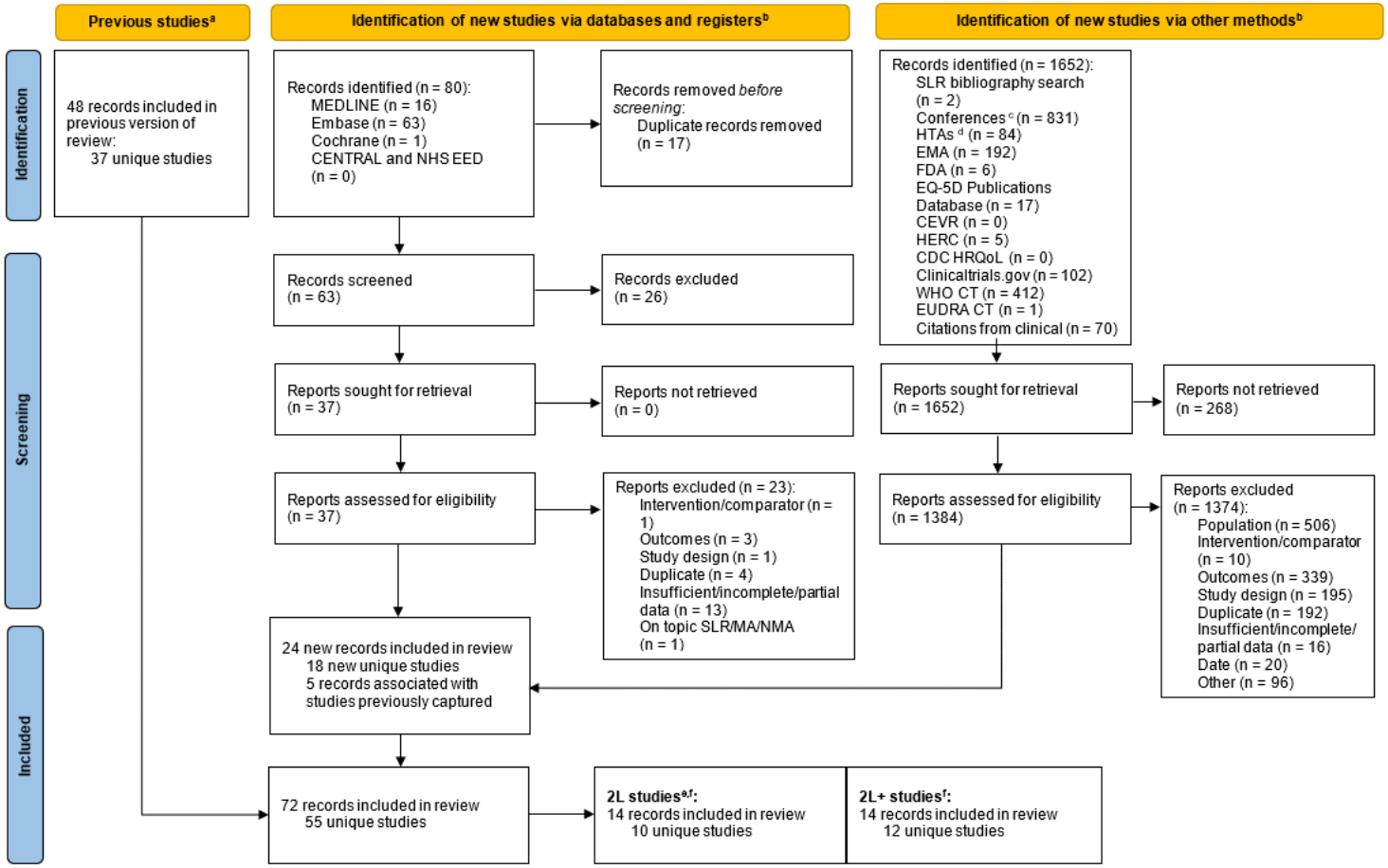
[a] Conferences searched included: American Association for Cancer Research (n=463), American Society of Clinical Oncology (n=1,636), American Society of Hematology (n=2,993), European Hematology Association (n=892), European Organisation for Research and Treatment of Cancer (n=16), European Society for Medical Oncology (n=563), International Society of Pharmacoeconomic and Outcomes Research (ISPOR; n=76), ISPOR EU (n=81), ISPOR APAC (n=9), and ISPOR LATAM (n=3).
[b] HTA sources searched included: Canadian Agency for Drugs and Technologies in Health (n=734), Health Technology Assessment International (n= 8), Institut National d'Excellence en Santé et Services Sociaux (n=49), National Institute for Health and Care Excellence (n=57), Pharmaceutical Benefits Advisory Committee (n=57), and Scottish Medicines Consortium (n=157).
[c] References lacking complete information for the PICOS criteria of interest.
[d] Conference abstracts identified in the database search, published prior to 2016.

A25. Please provide the full PRISMA flow diagrams for the health related quality of life searches carried out on the 8th June 2020 and updated on the 5th February 2021, 2nd May 2022 and 1st March 2023.

The PRISMA flow diagrams for the previous health-related quality of life (HRQoL) SLR updates are presented in Figure 10 to Figure 12**Error! Reference source not found.** as follows:

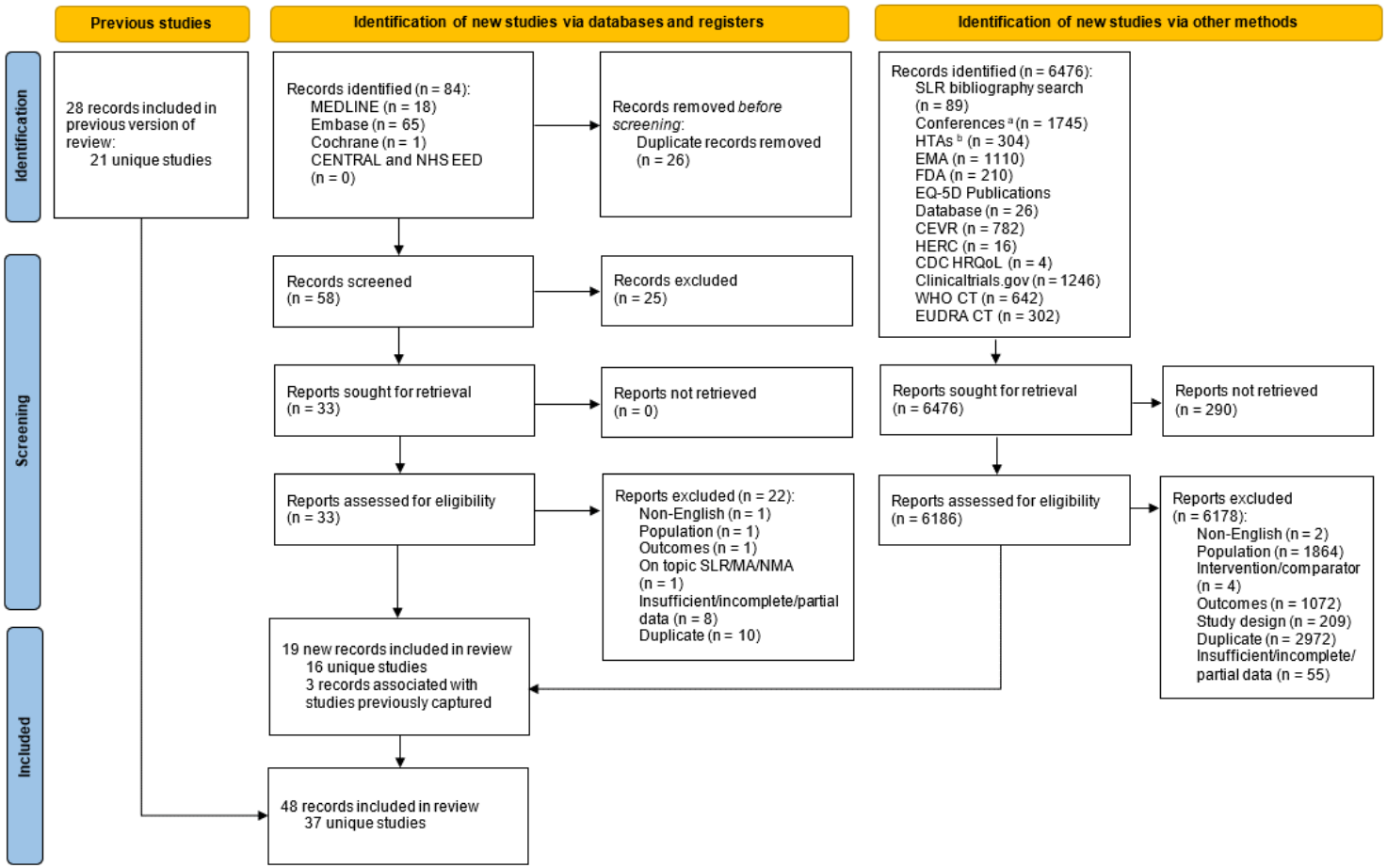
- **1st March 2023:** Figure 10
- **2nd May 2022:** Figure 11
- **8th June 2020 (original SLR search) and 5th February 2021 (update) combined:** Figure 12

Figure 10: PRISMA diagram for the March 2023 HRQoL evidence SLR



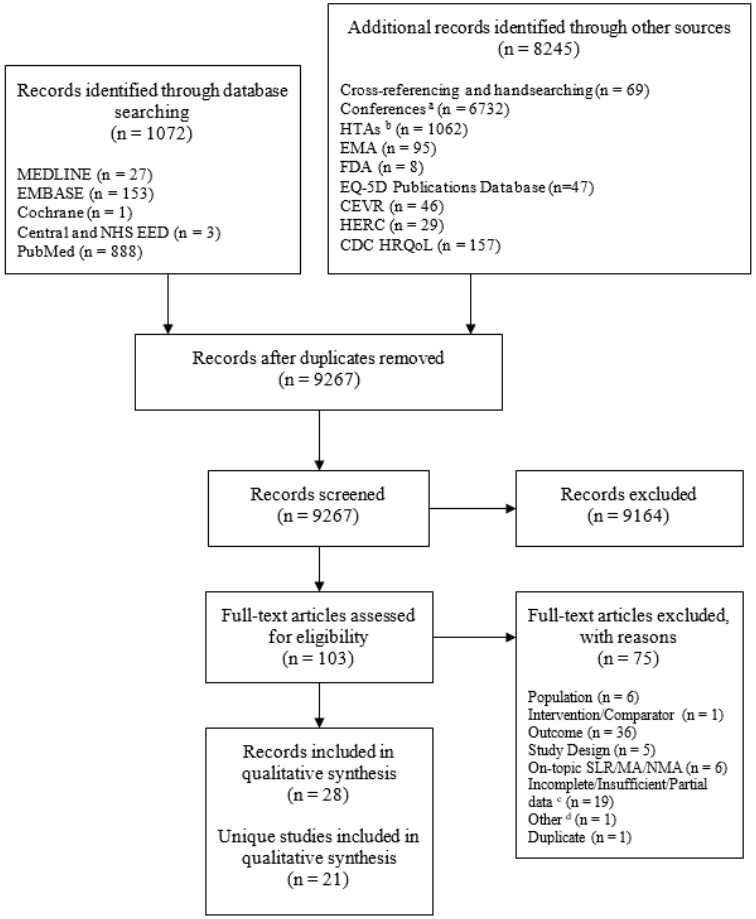
[a] 'Previous studies' refers to the studies identified in the 21st April 2020, 8th June 2020, 5th February 2021, 2nd May 2022 searches.
[b] 'Identification of new studies' refers to the present search conducted on 1st March 2023.
[c] Conferences searched included: American Association for Cancer Research (n=85), American Society of Hematology (n=691), European Organisation for Research and Treatment of Cancer (n=12), International Society of Pharmacoeconomic and Outcomes Research (n=19), International Workshop on non-Hodgkin Lymphoma (n=24).
[d] Sources of HTAs searched included: Canadian Agency for Drugs and Technologies in Health (n=27), Institut National d'Excellence en Santé et Services Sociaux (n=9), National Institute for Health and Care Excellence (n=14), Pharmaceutical Benefits Advisory Committee (n=25), and Scottish Medicines Consortium (n=9).
[e] Includes one utility study that reported outcomes for both a 2L and 3L+ subgroup.
[f] Includes one point in time survey that reported outcomes for both a 2L subgroup and an overall 2L+ population.

Figure 11: PRISMA diagram for the May 2022 HRQoL evidence SLR



[a] Conferences searched included: American Association for Cancer Research (n=426), American Society of Clinical Oncology (n=313), American Society of Hematology (n=745), European Hematology Association (n=178), European Society for Medical Oncology (n=33), International Society of Pharmacoeconomic and Outcomes Research (n=50).
[b] Sources of HTAs searched included: Canadian Agency for Drugs and Technologies in Health (n=22), Health Technology Assessment International (n=0), Institut National d'Excellence en Santé et Services Sociaux (n=64), National Institute for Health and Care Excellence (n=73), Pharmaceutical Benefits Advisory Committee (n=13), and Scottish Medicines Consortium (n=132).

Figure 12: Combined PRISMA diagram for the June 2020 HRQoL evidence SLR, including subsequent update in February 2021



[a] Conferences searched included: American Association for Cancer Research (n=463), American Society of Clinical Oncology (n=1,636), American Society of Hematology (n=2,993), European Hematology Association (n=892), European Organisation for Research and Treatment of Cancer (n=16), European Society for Medical Oncology (n=563), International Society of Pharmacoeconomic and Outcomes Research (ISPOR; n=76), ISPOR EU (n=81), ISPOR APAC (n=9), and ISPOR LATAM (n=3).
[b] HTA sources searched included: Canadian Agency for Drugs and Technologies in Health (n=734), Health Technology Assessment International (n=8), Institut National d'Excellence en Santé et Services Sociaux (n=49), National Institute for Health and Care Excellence (n=57), Pharmaceutical Benefits Advisory Committee (n=57), and Scottish Medicines Consortium (n=157).
[c] References lacking complete information for the PICOS criteria of interest.
[d] Conference abstracts identified in the database search, published prior to 2016.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please confirm how reimbursement for non-conforming product and manufacturing failure or otherwise fail to receive liso-cel following leukapheresis will be managed between the company and the NHS.

BMS can confirm that, excluding any applicable administration costs as previously mentioned in Section B.3.5.1 of the CS, there will be no charge to the NHS for the actual cost of any non-conforming liso-cel product or manufacturing failure for liso-cel that has not been infused to the patient.

B2. Priority question: Please explain why costs do not appear to be included for cases of manufacturing failure, non-conforming product or withdrawal.

As detailed in the CS Section B.3.5.1, [redacted] patient received an out-of-specification liso-cel product due to manufacturing failure in the TRANSFORM trial.[17, 32] For this patient, the costs associated with CAR-T acquisition were not accounted for, as it is assumed that these costs would be borne by BMS. All remaining associated costs, including CAR-T administration costs were included, as the CAR-T tariff cost was applied to these patients.

A total of [redacted] patients discontinued treatment prior to receiving lymphodepleting chemotherapy and did not receive infusion with liso-cel due to either manufacturing failure or non-measurable disease.[6] These patients were therefore assumed to accrue the costs of leukapheresis and bridging therapy only. Based on clinical feedback, these patients were not assumed to accrue the costs associated with any 2L treatment, but instead go on to receive the relevant subsequent therapy costs of the liso-cel arm.

B3. Priority question: Please implement in the economic model the functionality to use PFS without censoring for crossover, and PFS2 as alternatives to EFS to inform the model health states. (Please prioritise PFS2)

Changes to economic model to incorporate PFS-2

Due to time constraints, the functionality for the incorporation of PFS without censoring for crossover was not included and the incorporation of progression-free survival on subsequent line of therapy (PFS-2) was prioritised for inclusion instead. The incorporation of PFS-2 means the model health states are defined based on PFS-2 events instead of EFS events. The model is therefore partitioned into a pre-PFS-2 health state (encompassing patients receiving 2L and 3L treatment), a post-PFS-2 health state (i.e. fourth-line plus patients) and death.

The potential rationale for this approach is that, as patients are able to receive treatment with curative intent in both the 2L and 3L positions in the treatment pathway, disease progression on 3L treatment (i.e. PFS-2) potentially reflects the timepoint after which cure is no longer possible.

It should be noted that, in this scenario, PFS-2 is only used to determine health state occupancy, and therefore the applied utility value, over the model time horizon. Resource use costs are still applied based on the EFS curve in this scenario as the resource costs included in the model are directly related to the specific line of treatment. Similarly, subsequent treatment costs are still

applied based on time-to-next treatment (TTNT) in this scenario as these costs are tied specifically to the occurrence of this event.

Within this revised model structure, it is then necessary to consider the most appropriate utility values to inform the pre- and post- PFS-2 health states. In line with the Company base case, the EFS health state utility of 0.852 from the TRANSFORM trial was considered the most appropriate utility to inform the pre-PFS-2 health state. This inherently assumes that the receipt of HDCT and ASCT, or disease progression on 2L therapy, are associated with no detriment to patient HRQoL, which is potentially conservative.

However, the post-EFS event utility value of 0.808 used in the base case was based on a substantial proportion of patients receiving subsequent treatment ([redacted]%) who received 3L CAR-T cell therapy in the TRANSFORM trial, and as such, was considered unlikely to be representative of patients who have experienced disease progression on 3L treatment, and are unlikely to receive further treatment with curative intent.

Instead, the post-event utility value of 0.72 from TA895 was considered to represent a more appropriate utility input for the post-PFS-2 health state. The post-event utility value from TA895 was preferred by the NICE Committee to represent the utility value for patients who are no longer receiving with curative intent. At the time of TA895, this post-event utility value was for 3L patients who were not able to receive further treatment with CAR-T cell therapy in UK clinical practice. This post-EFS event utility value of 0.72 therefore represents a suitable input for the post-PFS-2 health state in this model, which similarly represents a population of patients who are no longer receiving treatment with curative intent.[33]

The utility values used to inform the pre- and post- PFS-2 health states are summarised in Table 14 below.

Table 14: PFS-2 scenario utilities

Health state	Utility (Mean)	Source
Pre PFS-2 event	0.852	TRANSFORM UK Utility analysis, 23 Oct 2023 DCO, Model H
Post PFS-2	0.72	Post progression utility final TA895 value, ZUMA-1 3L axi-cel trial[33]

Abbreviations: PFS-2: progression-free on next line of therapy.

Defining PFS-2 events

Compared to other indications, PFS-2 is challenging to measure for patients with R/R LBCL. In most oncology indications, patients experience disease progression on each line of treatment, before stopping treatment and progressing to the next line of therapy. However, for patients with LBCL, treatment is given with curative intent, and stable disease (SD) is not an acceptable outcome. This means that LBCL patients with a suboptimal response to treatment will be moved onto a new therapy for a potential cure at the earliest opportunity.[9] As such, patients do not necessarily experience disease progression on each line of treatment before switching to the next line of treatment, and for some patients, progression on 3L therapy may be the first time that they experience disease progression.

Definition of PFS-2 in TRANSFORM

In the TRANSFORM trial, PFS-2 was defined as time from randomisation to second objective

disease progression or death from any cause, whichever occurred first. However, only patients who experienced a first progression event were considered in this analysis, and deaths that occurred prior to disease progression were not considered.

In addition, under this definition, the timing of a PFS-2 event is misleading for patients who do not progress on their initial treatment, but progress on their subsequent treatment and die. The length of PFS-2 for these patients would be based on when they died, as this was defined as their PFS-2 event. However, it might be expected that the correct length of PFS-2 for these patients would be defined by their disease progression on 3L therapy, rather than their time to death. To account for this, patients who experienced progression on their subsequent treatment but did not progress on the first treatment were not considered to have two progression events, and therefore were not included in the PFS-2 analysis.

Considering these limitations, the TRANSFORM definition of PFS-2 was not considered appropriate for inclusion in the economic model.

Alternative PFS-2 analysis

An alternative, exploratory analysis for PFS-2 was conducted using the following definition: “the time from randomisation to disease progression on next-line of treatment (i.e. 3L treatment) or death, whichever occurs first.” This definition is more in line with typical PFS-2 definitions included in other oncology indications, and reflects the timepoint at which patients are unlikely to be treated with curative intent in either treatment arm.

The full ITT population of the TRANSFORM trial was considered in this analysis, meaning that unlike the TRANSFORM definition of PFS-2, patients were included regardless of whether they experienced disease progression on 2L treatment.

Extrapolation of PFS-2

The Kaplan-Meier (KM) curves for the revised PFS-2 analysis are presented in Figure 13. In both treatment arms, there is a sharp drop towards the end of the KM curves due to the limited number of patients remaining at this timepoint.

This is the result of another important limitation of PFS-2 – in the TRANSFORM trial, patients were only followed-up for disease progression for 36 months, after which point, patients were followed up for OS only. This means that, by definition, all patients were censored for PFS-2 at approximately 36 months, and so the only patients who remained at risk after this timepoint were patients who subsequently died. This results in the liso-cel PFS-2 KM dropping to 0% based on a single death event that occurred after 36 months, even though a substantial number of patients were still known to be alive after 36 months (as evidenced by the OS KM curve presented in CS Section B.2.6.3). The substantial majority of patients alive after 36 months are likely to be cured, based on the extremely poor prognosis for patients with R/R LBCL who are not cured, and therefore it is reasonable to assume that any patients who are still alive after 36 months would be unlikely to experience further disease progression.

For this reason, the PFS-2 data for both treatments must be interpreted with caution.

Figure 13: Kaplan-Meier plot for revised PFS-2 analysis, ITT

Abbreviations: KM: Kaplan-Meier; ITT: intention-to-treat; PFS-2: progression free survival on next line of therapy; SOC: standard of care.

Per the approach for EFS, OS and TTNT detailed in CS Section B.3.3.2, mixture cure models were fitted to PFS-2 data from the TRANSFORM trial in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14 and 21.[34, 35] The full range of parametric distributions were explored (exponential, Weibull, log-logistic, log-normal, Gompertz, gamma and generalised gamma). The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were estimated for each parametric function.

The log-logistic and log-normal curves for PFS-2 were selected for liso-cel and SOC, respectively, based on clinical plausibility and statistical fit, in line with the approach taken in CS Section B.3.3.2 for EFS, OS and TTNT. Further details of the curve selection are provided in Appendix B below.

Results

The deterministic and probabilistic results for this scenario using the revised PFS-2 for liso-cel (with PAS) versus SOC are presented Table 15 and Table 16, respectively.

The results of the scenario analysis indicated that the use of PFS-2 was generally consistent with the use of EFS in the base case economic model; the scenario using PFS-2 was associated with a small decrease in incremental QALYs compared to the base case ([redacted] versus [redacted]).

There are a number of limitations associated with this approach. Firstly, unlike the current base case approach using EFS, this approach assumes there would be no HRQoL detriment for patients who move from 2L to 3L treatment for any reason. This does not align with the data from the TRANSFORM trial, which showed that patients experience a utility decrement of approximately -0.04 upon experiencing an EFS event (based on a pre-EFS utility of 0.852 and a post-EFS utility of 0.808). Additionally, numerous studies in the published literature indicate that

the receipt of the current 2L SOC of re-induction therapy followed by HDCT and ASCT is associated with considerable detrimental impact on HRQoL, due to the risk of short- and long-term side effects.[36-38]

The final post progression utility value from TA895, based on the ZUMA-1 trial, is considered most appropriate to inform the post PFS-2 event health state, in line with the Committee's preferred assumptions in TA895.[33] However, this approach uses a utility value from an external trial and therefore differences in patient characteristics between the ZUMA-1 and TRANSFORM trials have not been accounted for in this analysis. Furthermore, in ZUMA-1, 10% of patients received 3L CAR-T so while the committee in TA895 agreed this utility value was representative of 3L patients who were not receiving 3L CAR-T, it is possible the utility value for patients who are no longer receiving treatment with curative intent is being overestimated.[9, 39]

In addition, the PFS-2 analysis is severely limited due to the discrepancies in follow-up between death and disease progression. In TRANSFORM, the final follow-up visit was conducted at approximately Month 36, at which point, patients were only followed up for OS. By definition, this means that patients were all censored in the analysis of PFS-2, as patients were no longer being assessed for disease progression.

However, the substantial majority of patients remaining alive at this time point are likely to be cured, given the extremely poor prognosis associated with LBCL that is not cured. As such, by censoring all patients at Month 36, this potentially underestimates PFS-2 given that many patients were known to be alive a number of months after this timepoint (see Figure 9 of CS). This also means that the single death event in the liso-cel arm occurring after Month 36 causes the KM curve to drop from over 50% to 0%, because patients are no longer being assessed for disease progression at this timepoint and therefore are no longer at risk. As shown by the extrapolations in Appendix B, this sudden drop of the KM leads to a wide range in survival estimates generated by the extrapolations and increases the uncertainty associated with this analysis.

Given the limitations associated with this analysis, the use of PFS-2 is associated with substantial additional uncertainty versus EFS, which is used in the Company base case economic analysis. The preference to use EFS to inform the model is because, in this indication, EFS is a more clinically relevant endpoint than PFS, given the curative intent of treatment. As highlighted by UK clinical experts, it is common practice in LBCL to move patients to the next line of therapy in this setting if their best response is SD, given the severe nature of the condition.[40] Clinical experts agreed EFS is a more clinically relevant endpoint and should be used to inform the economic model.[40] The use of EFS also aligns with previous NICE TAs in similar indications (TA895) and disease area (TA872) and with the primary endpoint in the TRANSFORM trial.[33, 39]

Table 15: Deterministic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case*		[redacted]	[redacted]	Dominant	2.65			
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.59	£0.00	-0.06	-0.06

*The base case results reported here differ slightly to the original CS base case as a correction has been made to include a half-cycle correction for subsequent treatment costs and end-of-life costs (see Appendix B).
Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Table 16: Probabilistic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	Dominant	2.51			
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.55	£0.00	-0.17	-0.17

*The base case results reported here differ slightly to the original CS base case as a correction has been made to include a half-cycle correction for subsequent treatment costs and end-of-life costs (see Appendix B).
Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

B4. Priority question: Please provide a summary of baseline characteristics that serve as model inputs (mean age, proportion of female patients, mean body weight and mean BSA as in Table 34 of the CS) for the following subgroups from TRANSFORM: DLBCL, PMBCL, FL3B, HGBCL.

A summary of the baseline characteristics informing the CEM for the subgroups of patients with diffuse large B cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) are provided in Table 17.

Table 17: Summary of baseline characteristics by NHL type

Characteristic	ITT analysis set (N=184)	DLBCL (N=118)	PMBCL (N=17)	FL3B (N=1)	HGBCL (N=43)
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of female patients, %	42.9	[redacted]	[redacted]	[redacted]	[redacted]
Mean body weight, kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BSA, m^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Based on n=180.
Abbreviations: BSA: body surface area; ITT: intention-to-treat; LBCL: large B-cell lymphoma.
Source: BMS Data on File: TRANSFORM Demographics Characteristics by B-cell NHL Type (October 2023 DCO).[12, 41]

B5. Priority question: Please implement weekly discounting for the duration of the model which uses a weekly cycle.

The implementation of weekly discounting (for the duration of the model that uses a weekly cycle length) has been conducted in the following scenario analysis. Deterministic and probabilistic results of this scenario analysis are presented in Table 18 and Table 19, respectively, and have a minimal impact on the overall economic results.

Table 18: Deterministic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case*		[redacted]	[redacted]	Dominant	[redacted]			
1	Clarification question, B.5: Weekly discounting	[redacted]	[redacted]	Dominant	[redacted]	£1,981	-0.01	-0.07

*The base case results reported here differ slightly to the original CS base case as a correction has been made to include a half-cycle correction for subsequent treatment costs and end-of-life costs (see Appendix A).
Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Table 19: Probabilistic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	Dominant	[redacted]			
1	Clarification question, B.5: Weekly discounting	[redacted]	[redacted]	Dominant	[redacted]	£1,930	-0.01	-0.07

*The base case results reported here differ slightly to the original CS base case as a correction has been made to include a half-cycle correction for subsequent treatment costs and end-of-life costs (see Appendix A).
Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

B6. Priority question: Please provide more detail on how the utility values for the overall population (both event free and post-event) was calculated including the timepoints included and any statistical model used and its output.

The EuroQol 5-Dimension (EQ-5D) utility analyses considered all patients from the HRQoL (EQ-5D-5L) analysis set in TRANSFORM. This represented a subset of patients from the ITT analysis set with both a baseline EQ-5D utility and at least one follow-up visit with complete EQ-5D utility. Of the 184 patients in the ITT analysis set in TRANSFORM, approximately half ([redacted] [redacted]%]) were included in the EQ-5D analysis set. The compliance rate for completing EQ-5D questionnaires was relatively low (i.e. [redacted]%), partially because of operational issues experienced during the COVID-19 pandemic.

The baseline characteristics of the ITT and EQ-5D analysis populations were generally comparable. For each response to the EQ-5D questionnaire collected in TRANSFORM, five-digit EQ-5D-5L health states were derived by concatenating the levels, or response options, from each of the five dimensions included in the EQ-5D questionnaire. That is, responses to the five domains of the EQ-5D questionnaire were combined to create a five-digit EQ-5D health state (e.g., 11111). In total, there are 3,125 unique health states reflecting all possible combinations of the five health domains and five severity levels. In line with the requirements specified in the NICE manual for health technology evaluations (31 January 2022),[42] the mapping function developed by Hernández Alava et al. (2022) using the "EEPRU" data set[43, 44] was implemented to crosswalk between an EQ-5D-3L value set for the UK and EQ-5D-5L health states collected in TRANSFORM.

The cross-walked EQ-5D utility scores for the UK were analysed using linear mixed-effects models, fit according to the *lme4* package in R.[45] Because the aim of this analysis was to derive a predictive equation to be used in the CEM, only predictors that are relevant to the health states and events captured in the CEM were considered.

All regression analyses adjusted for baseline utility (centred at the mean value of the EQ-5D evaluable population) as a fixed effect, to consider between-patient differences in utilities at baseline. By including baseline utility as a predictor in all univariate and multivariate models, these EQ-5D analyses are mathematically equivalent to a change from baseline analysis. In addition to baseline utilities, the candidate predictors were evaluated in univariate regression analyses. Details on the univariate regression analyses performed are presented in Appendix C of this response.

Eight multivariate models were developed and compared to determine the best-fitting model based on information criteria (AIC and BIC) to inform the CEM (Table 20). The candidate predictors included for each multivariate model is summarised in Table 38 of Appendix C.

Note that the statistical models being compared according to AIC/BIC should be fit according to the same sample; for instance, models F and G were fit to data of different sample sizes and cannot be compared on the basis of AIC and BIC. Model H was selected as the final model to inform the CEM for several reasons: (1) best-fitting among models D, E, G, and H according to AIC, and comparable according to BIC; (2) one of the more parsimonious models, including four predictors; (3) all predictors were statistically significant (P<0.05); (4) captures the most salient health states and events in the CEM; and (5) the model fit the observed data well according to

visual inspection of predicted versus observed utilities.

The candidate predictors included in Model H are as follows:

- Centred baseline utility
- Liso-cel pretreatment: lymphodepleting chemo
- Event-free status
- Other grade 3+ AE

Table 20: Comparison of AIC/BIC fit statistics for multivariate utility models

Multivariate model	Number of predictors	Significant predictors (*P*<0.05)?	Number of observations	AIC	BIC
A	6	Baseline utility	[redacted]	[redacted]	[redacted]
B	4	Baseline utility, LDC	[redacted]	[redacted]	[redacted]
C	3	Baseline utility	[redacted]	[redacted]	[redacted]
D	5	Baseline utility, EFS, grade 3+ AE	[redacted]	[redacted]	[redacted]
E	4	Baseline utility, EFS, grade 3+ AE	[redacted]	[redacted]	[redacted]
F	3	Baseline utility, grade 3+ AE	[redacted]	[redacted]	[redacted]
G	3	Baseline utility, EFS, grade 3+ AE	[redacted]	[redacted]	[redacted]
H	**4**	**Baseline utility, EFS, grade 3+ AE, LDC**	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; AIC: Akaike information criterion; BIC: Bayesian information criterion; EFS: event-free survival; LDC: lymphodepleting chemotherapy
Footnotes: Models A, B, C, and F (grey shaded rows) were fit to the same sample of observations (n=418), and therefore the AIC/BIC fit statistics for these models can be compared. Similarly, models D, E, G, and H (unshaded rows) were fit to the same sample of 410 observations, which allows for comparison of AIC/BIC fit across these three models.

In addition to fit AIC/BIC statistics, multivariate model H was validated via visual inspection. The predicted mean utilities (95% CIs) closely aligned with the observed mean utilities (95% CI), stratified by health states (Figure 14). Mean predictions were plotted according to the (1) fixed-effects portion of the regression model and (2) the fixed effects plus random effects of the regression model. In general, the addition of random effects improves the fit to the observed data.

Figure 14: Comparison of the predicted mean utilities (based on multivariate model H) versus the observed mean utilities in TRANSFORM, stratified by health states

Abbreviations: AE: adverse event; EF: event-free; LDC: lymphodepleting chemotherapy.

The estimated regression coefficients for the fixed effects included in multivariate model H are summarised in Table 21 . The numbers of patients and observations contributing to each health state included in the model are summarised in Table 21. Multivariate model H was fit to a total of [redacted] observations; of these, [redacted] were recorded post-EFS and [redacted] were collected during an ongoing Grade 3+ AE.

Table 21: Final multivariate utility model (H) used to inform CEM inputs

	Number		$\hat{\beta}$	SE	95% CI		*P* value
	Patients	Observations			Lower bound	Upper bound	
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Centred baseline utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-EFS event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; CEM: cost-effectiveness model; EFS: event-free survival; LDC: lymphodepleting chemotherapy.

The average marginal means, also known least-squares means, were estimated for each health state according to the g-computation method (Table 22).[46] For each health state, the average marginal mean is simply the linear combination of relevant coefficients presented in Table 21.

The average marginal means presented in Table 22 represent the health state utility inputs used in the base case cost-effectiveness analyses. The AE-free utilities were used in the economic model as the impact of AEs on HRQoL were considered separately; the model additionally applied a one-time utility decrement ([redacted]) for patients who received lymphodepleting chemotherapy before infusion with liso-cel (as detailed in Section B.3.4 of Document B).

Table 22: Health state marginal means (multivariate model H) – Inputs in the UK CEM

Health state (No LDC)	Marginal mean	SE	95% CI	
			Lower bound	Upper bound
Event-free and AE-free	0.852	[redacted]	[redacted]	[redacted]
Post-EFS event and AE free	0.808	[redacted]	[redacted]	[redacted]
Event-free and ongoing grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]
Post-EFS event and ongoing grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; EFS: event-free survival; LDC: lymphodepleting chemotherapy.

B7. Priority question: Please provide detail on the TTNT outcome, and how events were defined, how time-to-event was calculated, and what censoring rules were applied.

TTNT data were utilised in the base case CEM to determine the timepoint for initiation of subsequent therapy and the proportion of patients receiving subsequent treatment in both the liso-cel and SOC arms, in line with the approach taken in TA895.[33] The costs of subsequent therapy were applied as a single one-off cost for patients in the post-event health state based on the TTNT curve. This represents a simplifying assumption, which aims to apply subsequent treatment costs on a time-dependent basis, as the time spent in the post-event health state is not easily able to be tracked within the cost-effectiveness model. As the duration of subsequent treatment is generally less than a year, this simplifying assumption was expected to have a negligible impact on the modelled results.

TTNT was defined as the time from randomisation to death due to any cause or start of new antineoplastic therapy, whichever occurred first. The event and censoring rules used for the TTNT outcome are listed in Table 23. Full details of the extrapolation of the TTNT data from TRANSFORM are provided in the CS, Section B.3.3.5.

Table 23: Event and censoring rules for TTNT

Situation	Date patient has event or is censored	Situation outcome
Death	Death date	Event
Start of a new antineoplastic therapy due to efficacy concerns	Therapy start date	Event
Start of a new antineoplastic therapy for reasons other than efficacy concerns	Therapy start date	Event
No death, no start of new antineoplastic therapy	Last known alive date	Censor

Abbreviations: TTNT: time-to-next treatment.

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Appendix A: Updated model results

As part of the clarification questions, two corrections have been made to the submitted economic model results:

- The inclusion of a half-cycle correction for subsequent treatment costs and end-of-life costs (not previously included in the original CS base case). This results in a change to incremental costs of £8.
- In the original CS model, the subsequent treatment costs in Scenario analysis #13 for epcoritamab were incorrectly applied for 9.1 3-week cycles instead of 4-week cycles. This did not impact the original CS base case and only impacts the scenario utilising the clinician subsequent treatment distribution estimates. The subsequent treatment duration of epcoritamab has been updated to 9.1 4-week cycles in the CQs model with the updated results of the affected scenario are presented in Table 32

The updated deterministic base case results, along with the results of the probabilistic and deterministic sensitivity analyses and scenario analyses are presented in the below sections, including these corrections.

Base case results

The updated base case deterministic and probabilistic cost-effectiveness results for liso-cel (with PAS) versus SOC are presented in Table 24 and Table 25, respectively.

Table 24: Deterministic base-case results (liso-cel PAS price)

Treatment	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	NHB at £20,000/QALY WTP threshold	NHB at £30,000/QALY WTP threshold
Liso-cel	[redacted]	10.29	[redacted]	[redacted]	1.50	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	8.78	[redacted]						

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Table 25: Probabilistic base-case results (liso-cel PAS price)

Treatment	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	NHB at £20,000/QALY WTP threshold	NHB at £30,000/QALY WTP threshold
Liso-cel	[redacted]	10.20	[redacted]	[redacted]	1.46	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	8.74	[redacted]						

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Disaggregated results of the base case incremental cost-effectiveness analysis

Disaggregated results of the updated deterministic base case are presented in Table 26 to Table 28 below. The equivalent disaggregated results of the probabilistic base case are presented in Table 29 to Table 31.

Table 26: Deterministic base case disaggregated QALYs by health state

Health state	QALY Liso-cel	QALY SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L treatment-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; QALY: quality-adjusted life year; SOC: standard of care

Table 27: Deterministic base case disaggregated costs by health state

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; SOC: standard of care.

Table 28: Deterministic base case disaggregated costs by resource type

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Primary treatment acquisition cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary treatment administration cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment administration cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE management and IVIG (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (EF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (Post-event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; EF: event-free; IVIG: intravenous immunoglobulin; SOC: standard of care.

Probabilistic sensitivity analysis

The scatter plot showing the incremental costs and QALYs for liso-cel at PAS price compared with SOC is presented in Figure 15, respectively.

Figure 15: Cost-effectiveness plane: liso-cel (PAS price) versus SOC

Footnotes: The cost-effectiveness plane includes a WTP of £30,000/QALY.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care; WTP: willingness-to-pay.

Cost-effectiveness acceptability curves for liso-cel at PAS price when compared with SOC are presented in Figure 16, respectively. At a WTP threshold of £20,000 and £30,000 per QALY gained and using a PAS for liso-cel and list price for all other modelled treatments, the PSA found the probability of liso-cel being a cost-effective use of NHS resource to be [redacted]% and [redacted]%, respectively. At a WTP threshold of £20,000 and £30,000 per QALY gained and using a PAS for liso-cel and list price for all other modelled treatments, the PSA found the probability of liso-cel being a cost-

effective use of NHS resource to be [redacted]% and [redacted], respectively.

Figure 16: Cost-effectiveness acceptability curve: liso-cel (PAS price) versus SOC

Abbreviations: PAS: patient access scheme; SOC: standard of care.

Table 29: Probabilistic base case disaggregated QALYs by health state

Health state	QALY Liso-cel	QALY SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L treatment-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; QALY: quality-adjusted life year; SOC: standard of care

Table 30: Probabilistic base case disaggregated costs by health state

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Event-free (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post event (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; SOC: standard of care.

Table 31: Probabilistic base case disaggregated costs by resource type

Health state	Cost Liso-cel	Cost SOC	Increment	Absolute Increment	% Absolute Increment
Primary treatment acquisition cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary treatment administration cost (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment administration cost (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE management and IVIG (2L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (EF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use (Post-event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line plus; AE: adverse event; EF: event-free; IVIG: intravenous immunoglobulin; SOC: standard of care.

Deterministic sensitivity analysis

The tornado diagram showing the top 10 most influential parameters on ICER for liso-cel at PAS price versus SOC is presented in Figure 17.

Figure 17: Tornado diagram of the ten most influential parameters from the DSA: liso-cel (PAS price) versus SOC

Abbreviations: DSA: deterministic sensitivity analysis; PAS: patient access scheme; SOC: standard of care.

Scenario analysis

The results of the updated probabilistic scenario analyses are presented in Table 32.

Table 32: Summary of scenario analysis results (probabilistic)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	Dominant	2.51			
1	EFS extrapolation (liso-cel): log-logistic	[redacted]	[redacted]	Dominant	2.51	-£40	0.00	0.00
2	EFS extrapolation (SOC): generalised gamma	[redacted]	[redacted]	Dominant	2.52	£10	0.01	0.00
3	OS extrapolation (liso-cel): generalised gamma	[redacted]	[redacted]	Dominant	2.77	-£41	0.25	0.25
4	OS extrapolation (liso-cel): Weibull	[redacted]	[redacted]	Dominant	2.74	-£63	0.23	0.23
5	OS extrapolation (SOC): TRANSFORM/CORAL mix	[redacted]	[redacted]	Dominant	3.04	£130	0.53	0.53
6	TTNT extrapolation (liso-cel): log-logistic	[redacted]	[redacted]	Dominant	2.51	£30	0.00	0.00
7	TTNT extrapolation (SOC): log-logistic	[redacted]	[redacted]	Dominant	2.51	£59	0.00	0.00
8	Utility values: TA895	[redacted]	[redacted]	Dominant	2.66	£0	0.15	0.15
9	Cure timepoint: 2 years	[redacted]	[redacted]	Dominant	2.53	-£520	0.00	0.02
10	CAR-T costs: adjusted CAR-T tariff	[redacted]	[redacted]	Dominant	2.61	-£2,876	0.00	0.10
11	Bridging therapy distribution: UK clinical expert opinion	[redacted]	[redacted]	Dominant	2.48	£801	0.00	-0.03
12	SOC distribution: UK clinical expert opinion	[redacted]	[redacted]	Dominant	2.39	£3,636	0.00	-0.12
13	Subsequent therapies: Distribution based on UK clinical expert opinion, Weibull curve for liso-cel OS and SOC OS based on TRANSFORM/CORAL	[redacted]	[redacted]	Dominant	2.16	£33,220	0.76	-0.35

	(using log-normal and gamma curves, respectively)							
14	Clarification Question B5 – Per-cycle discounting	[redacted]	[redacted]	Dominant	2.44	£1,930	-0.01	-0.07
15	Clarification Question B3 – Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.34	£0	-0.17	-0.17

Abbreviations: EFS: event-free survival; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYs: life years; OS: overall survival; QALYs: quality-adjusted life years; TTNT: time to next treatment; SOC: standard of care.

Appendix B: Curve selection

Liso-cel

The extrapolations of PFS-2 for each parametric model up to 5 years are presented in Figure 18, with long-term extrapolations up to 15 years presented in Figure 19. Extrapolations of PFS-2 for non-cured patients only is presented in Figure 23. AIC/BIC values for each extrapolation are presented in Table 33. The predicted cure fractions and projections of PFS-2 for non-cured patients only for each extrapolation are presented in Table 34.

Visual inspection shows that all extrapolations had good visual fit to the KM curve from TRANSFORM, however, there was a large degree of variation in survival estimates across the various models. As shown in Figure 19, the generalised gamma, gamma, exponential and Gompertz curves all generated pessimistic estimates of long-term survival compared to the Log-normal, loglogistic and Weibull curves. This was likely due to the limitations associated with the censoring of the PFS-2 endpoint, as detailed in B3. The lack of cure estimated by these curves and pessimistic survival estimates were considered clinically implausible, given the majority of patients would have been treated with CAR-T. The generalised gamma, gamma, exponential and Gompertz curves were therefore excluded from consideration.

The remaining curves all generated similar estimates of long-term survival for the cured and non-cured population and therefore the clinical plausibility of the estimates for survival for the non-cured patients was considered. In TA895, clinical experts noted that patients who relapse would do so within 2 years.[33] Therefore, it was assumed any curves that estimated EFS to be higher than ~10% after 2 years were considered to be clinically implausible.[33] In line with this approach, but accounting for the additional follow-up needed to observe PFS-2 events, it was assumed the majority of non-cured patients would die within 4 years and less than ~10% of patients would be PFS-2 at approximately 4 years. Only the Weibull and log-logistic estimated less than 10% of patients would be PFS-2 after 4 years. The log-logistic curve was selected in the base-case, as it was the better fitting model according to AIC ([redacted]; rank: 3) and BIC ([redacted]; rank 4) compared to the Weibull.

Figure 18: Short-term extrapolations of PFS-2 for liso-cel for cured and non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy.

Figure 19: Long-term extrapolations of PFS-2 for liso-cel for cured and non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy

Figure 20: Extrapolation of PFS-2 for liso-cel for non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy

Table 33: AIC and BIC statistics, PFS-2 for liso-cel

Curve	Statistical fit			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	4	[redacted]	2
Weibull	[redacted]	6	[redacted]	6
Log-normal	[redacted]	2	[redacted]	1
Log-logistic	[redacted]	3	[redacted]	4
Gompertz	[redacted]	7	[redacted]	7
Generalised gamma	[redacted]	1	[redacted]	3
Gamma	[redacted]	5	[redacted]	5

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 34: Model estimates of PFS-2 for liso-cel

Category	Curve	Cure fraction	PFS-2 % for cured and non-cured patients					PFS-2 % for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
TRANSFORM Data	TRANSFORM PFS-2 KM	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; NR: not reported; PFS-2: progression-free survival on next line of therapy.

SOC

The extrapolations of PFS-2 for each parametric model up to 5 years are presented in Figure 21, with long-term extrapolations up to 15 years presented in Figure 22. Extrapolations of PFS-2 for non-cured patients only is presented in Figure 23. AIC/BIC values for each extrapolation are presented in Table 35. The predicted cure fractions and projections of PFS-2 for non-cured patients only for each extrapolation are presented in Table 36.

Visual inspection shows that all extrapolations had good visual fit to the KM curve from TRANSFORM and there is a low degree of variation in survival estimates across the various models. All extrapolations generated broadly similar estimates of long-term survival (range: [redacted] at 15 years). The choice of curve for the base-case was therefore based on consideration of the plausibility of the extrapolations of non-cured patients, alignment with the cure fraction predictions from clinicians and statistical fit to the observed KM data from TRANSFORM.

Per the approach taken for liso-cel, it was assumed the majority of non-cured patients would die within 4 years and less than ~10% of patients would be PFS-2 at approximately 4 years. Both the generalised gamma and exponential curves estimated PFS-2 for non-cured patients to be greater than 10% at Year 4, and therefore were excluded from consideration.

Out of the remaining curves, the log-normal curve was selected for the base case as it was the best fitting model according to AIC ([redacted]; rank: 2) and BIC ([redacted]; rank 1) (once the Generalised Gamma was excluded).

Figure 21: Short-term extrapolations of PFS-2 for SOC for cured and non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy; SOC; standard of care.

Figure 22: Long-term extrapolations of PFS-2 for SOC for cured and non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy; SOC; standard of care.

Figure 23: Extrapolation of PFS-2 for SOC for non-cured patients

Abbreviations: KM: Kaplan-Meier; PFS-2: progression-free survival on next line of therapy; SOC; standard of care.

Table 35: AIC and BIC statistics, PFS-2 for SOC

Curve	Statistical fit			
	AIC	Rank	BIC	Rank
Exponential	[redacted]	4	[redacted]	3
Weibull	[redacted]	7	[redacted]	7
Log-normal	[redacted]	2	[redacted]	1
Log-logistic	[redacted]	3	[redacted]	4
Gompertz	[redacted]	5	[redacted]	5
Generalised gamma	[redacted]	1	[redacted]	2
Gamma	[redacted]	6	[redacted]	6

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; SOC; standard of care.

Table 36: Model estimates of PFS-2 for SOC

Category	Curve	Cure fraction	PFS-2 % for cured and non-cured patients					PFS-2 % for non-cured patients				
			1	2	5	10	15	1	2	3	4	5
TRANSFORM data	TRANSFORM PFS-2 KM	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolations	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates base case curve.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; NA: not applicable; NR: not reported; PFS-2: progression-free survival on next line of therapy; SOC: standard of care

Appendix C: Further details on derivation of utility values

Candidate predictors included in the univariate regression analyses are summarised in Table 37.

Table 37: Summary of candidate predictors included in univariate regression analyses

Predictor	Type of variable	Description
Baseline utility	Continuous, fixed	Centred at mean value Included in all univariate and multivariate analyses
Baseline age	Continuous, fixed	Centred at mean value
Sex	Binary, fixed	Male vs. female
Randomised treatment	Binary, fixed	SOC vs. liso-cel
Lymphodepleting chemo	Binary, time-varying	Check whether lymphodepleting chemo was received as a liso-cel pre-treatment at current visit
Bridging therapy	Binary, time-varying	Check whether bridging therapy was received as a liso-cel pre-treatment at current visit
Liso-cel location of administration	Binary, fixed	Inpatient vs. outpatient
Best overall response to first-line therapy	Binary, fixed	Relapse vs. refractory Stratification factor in TRANSFORM
sAAIPI score	Binary, fixed	2-3 vs. 0-1 Stratification factor in TRANSFORM
Event-free status	Binary, time-varying	Experienced event (post-EFS) vs. event-free EQ-5D values collected after censoring for EFS were excluded from analyses
HDCT + ASCT	Binary, time-varying	Received HDCT + ASCT vs. none
Cytokine release syndrome	Binary, time-varying	Ongoing Grade 3+ AE vs. none
Infection	Binary, time-varying	Ongoing Grade 3+ AE vs. none
Neurotoxicity	Binary, time-varying	Ongoing Grade 3+ AE vs. none
Prolonged cytopenia	Binary, time-varying	Ongoing Grade 3+ AE vs. none 35 days after liso-cel infusion (liso-cel arm) or 35 days after the start of the last cycle of chemotherapy (SOC arm)
Other Grade 3+ AE	Binary, time-varying	Ongoing Grade 3+ AE vs. none

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplantation; EFS: event-free survival; HDCT: high-dose chemotherapy; liso-cel: lisocabtagene maraleucel; sAAIPI: second-line age-adjusted International Prognostic Index; SOC: standard of care.

Given the timing of assessments in TRANSFORM, it was not possible to capture the anticipated utility impacts of all relevant events (e.g., transient disutility due to high-dose chemotherapy [HDCT] + ASCT). In the TRANSFORM trial, patients were assessed at the 9-week (Day 64) visit for response, at which point they were eligible for the HDCT + ASCT regimen if a complete or partial response was achieved. Initiation of HDCT + ASCT occurred about a week after the response assessment (Day 71). Because the first EQ-5D assessment after HDCT + ASCT initiation does not take place until Day 126, the short-term impact of HDCT + ASCT is not likely to be reflected in the trial data.

All continuous fixed effects (i.e., baseline age and utilities) were centred. A value of zero represents a patient with average baseline utility. Therefore, the intercept term of the model

corresponds to an “average” patient in the TRANSFORM trial. In regression models that included event-free status as a predictor, EQ-5D values that were collected after censoring for EFS were excluded, because in these cases, the patients’ progression status cannot be determined after the censoring date.

The initial set of regression analyses focused on assessing the univariate relationship between utility scores and the individual variables listed above, and the aim was to identify independent predictors of utility. The predictors considered in the multivariate regression models were based on the findings of the exploratory analyses of univariate relationships, and specific consideration was given to whether predictors were statistically significant when tested in univariate analysis, AIC/BIC fit statistics, and the specific health states and events captured in the cost-effectiveness model. A series of 16 univariate analyses were conducted, followed by eight multivariate models (Table 38**Error! Reference source not found.**). Multivariate model A was fit to control for differences in baseline characteristics between treatments (age and sex), including the two stratification factors used for randomisation in TRANSFORM. These factors were dropped in subsequent multivariate analyses because they were not predictive of utility scores.

Output from the regression analyses included the parameter estimates of fitted coefficients (mean, standard error [SE], 95% confidence interval [CI], *P* value, etc.), and the variance–covariance matrix for the fixed-effects parameters. The number of patients and observations contributing to the estimation of each regression coefficient were reported in the model summary tables. To assess goodness of fit of the regression models, plots of fitted versus observed utility values were generated in addition to fit statistics (AIC/BIC).

Table 38: Summary of candidate regression models

Predictor	Univariate	Multivariate model							
		A	B	C	D	E	F	G	H
Centred baseline utility[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Centred baseline age	✓	✓							
Sex	✓	✓							
Randomised treatment	✓	✓	✓	✓	✓	✓	✓		
Liso-cel pretreatment: lymphodepleting chemo	✓		✓						✓
Liso-cel pretreatment: Bridging therapy	✓		✓						
Liso-cel location of administration	✓								
Best overall response to first-line therapy	✓	✓							
sAAIPI Score	✓	✓							
Event-free status	✓				✓	✓		✓	✓
HDCT + ASCT	✓			✓	✓				
Cytokine release syndrome	✓								
Infection	✓								
Neurotoxicity	✓								
Prolonged cytopenia	✓								

Other Grade 3+ AE	✓				✓	✓	✓	✓	✓

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplantation; HDCT: high-dose chemotherapy; liso-cel: lisocabtagene maraleucel; sAAIPI: second-line age-adjusted International Prognostic Index
Footnotes: [a]All univariate and multivariate regression models included baseline utility as a predictor.

The coefficient estimates along with the associated standard errors and *P* values from the univariate analyses are summarised in Table 39**Error! Reference source not found.**. All of the univariate models except the analysis for EFS were fit to 418 post-baseline observations, collected from 94 patients in total. The univariate model for EFS was fit to 410 post-baseline observations (of 93 patients), because 8 of the EQ-5D responses were collected after EFS censoring.

The majority of the candidate predictors were not statistically significant. In particular, the difference in mean utilities was not statistically significant between treatments (*P*=0.0573). Experiencing an "other" Grade 3+ AE (i.e., excluding cytokine release syndrome, infection, neurotoxicity, prolonged cytopenia) was associated with a statistically significant reduction in mean utility of [redacted] (*P*=[redacted]).

Table 39: Summary of univariate utility models

Predictor	Number of patients (Observations)	Coefficient ($\hat{\beta}$)[a]	Standard error	*P* value
Centred baseline age	[redacted]	[redacted]	[redacted]	[redacted]
Sex (male vs. female)	[redacted]	[redacted]	[redacted]	[redacted]
Randomised treatment (SOC vs. liso-cel)	[redacted]	[redacted]	[redacted]	[redacted]
Liso-cel pretreatment: lymphodepleting chemo	[redacted]	[redacted]	[redacted]	[redacted]
Liso-cel pre-treatment: Bridging therapy	[redacted]	[redacted]	[redacted]	[redacted]
Liso-cel location of administration (inpatient vs. outpatient)	[redacted]	[redacted]	[redacted]	[redacted]
Best overall response to first-line therapy (relapse vs. refractory)	[redacted]	[redacted]	[redacted]	[redacted]
sAAIPI Score (2+ vs. 0-1)	[redacted]	[redacted]	[redacted]	[redacted]
Event-free status (experienced event vs. none)	[redacted]	[redacted]	[redacted]	[redacted]
HDCT + ASCT	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Infection	[redacted]	[redacted]	[redacted]	[redacted]
Neurotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged cytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Other grade 3+ AE	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; HDCT: high-dose chemotherapy; liso-cel: lisocabtagene maraleucel; NE: not estimable; sAAIPI: second-line age-adjusted International Prognostic Index
Footnotes: [a]All univariate regression models included baseline utility as a predictor. Baseline utility was a [redacted] in all univariate analyses. [b]No events coincided with EQ-5D responses.

Estimating a disutility was not possible for all AEs of interest because of the low incidence rates

observed in TRANSFORM. For cytokine release syndrome and neurotoxicity, no events coinciding with EQ-5D responses were recorded in TRANSFORM. Additionally, only three patients experienced a grade 3+ infection, and thus the estimated disutility is highly uncertain. Time windows before the onset and after the resolution (if resolved) of toxicity events were also tested because symptoms may occur earlier than the onset date, and the effects of experiencing AE Grade 3+ on quality of life may linger for a period of time after resolution. However, even with the consideration of time windows, it was still not possible to reliably estimate disutilities for cytokine release syndrome, infection, and neurotoxicity because of the low incidence rates.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is a blood cancer research charity. We fund research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has ~120 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Yes. We received £466,192 from Bristol-Myers Squibb for a project on 'Improving awareness and access to clinical trials for ethnic minority communities' and £35,000 for development of the Blood Cancer Action Plan.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and	The information for this appraisal was gathered from insights derived through our communications with the clinical, research and patient community, particularly those personally affected by the various lymphoma subtypes of interest here. We also spoke to patients who have received Lisocabtagene maraleucel and to those with experience of caring

carers to include in your submission?	for the patient group of interest. Blood Cancer UK has close relationships and maintains regular contact with the haemato-oncology community. We do this through our Healthcare Professional Advisory Panel (HPAP), Nurses Working Group (NWG), our patient ambassador network etc. We additionally maintain relationships with many other blood cancer specialists – from research nurses to academic researchers – through our Information and Support, Research, and Policy, Campaigns, and Involvement teams. We specifically reached the patient group of interest for this appraisal through our clinical networks who put us in touch with patients willing to share their experiences of the technology with us. We conducted hour long interviews with them exploring their experiences. We have also included information based on our previous conversations with people who have large B-cell lymphoma. These conversations built our understanding of the experiences of those affected by the issues of interest for this appraisal.

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?	The subtypes of lymphoma being considered for this appraisal cause differing symptoms of varying intensity for patients diagnosed with it. Large B-cell lymphomas are aggressive cancers which can progress rapidly and make people feel unwell with a significant and immediate impact on life. A consultant haematologist expresses how it can often be effectively treated, and treatments have a curative intent although this is only achieved in approximately 50% of cases with a wide variation depending on age, fitness, type of lymphoma and genetic risk factors among others. One person stated that having lymphoma is like 'playing health snakes and ladders.' She explains that 'as the disease progresses, one falls down a snake and if a treatment is successful, one climbs back gradually to normal life. There will be another snake and with luck, another ladder.' She went on to explain that it is challenging knowing that 'at some point, one will fall down a snake with no ladder to get back up. Another person explained that frequent blood tests, extreme fatigue, compromised immunity, constant uncertainty, bone marrow biopsies and constantly worrying about the effects of the illness on family are all part of living with lymphoma. There is a heavy burden borne by patients and carers who experience refractory/relapse disease in both managing symptoms of the disease combined with the toxicity of treatments. Carers play a critical role in patients' disease and treatment journey and caring for someone with large B-cell lymphoma is often challenging and burdensome. Carers are fundamental to a patient's day to day wellbeing, helping with everything from transportation, managing appointments to their nutritional need. Carers must often plan their lives around treatments and take a bigger share of the domestic load, all while constantly worrying about their loved one.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with primary refractory or early relapsed large B-cell lymphoma view the current standard of care on the NHS as suboptimal. Although they are grateful for the available options, existing treatments can be hard to tolerate, bringing a range of side effects and late effects. One person we spoke to described that conventional treatment cycles lead to prolonged hospital stays, endless blood tests, platelet transfusions and other life-saving drugs. Although first line treatment can induce remissions for some, these remissions are often relatively short-lived. The patients we spoke to described it as 'a short-term fix.' Treatments like chemotherapies can "wreck" the body and make it harder to tolerate further treatment. Many existing treatments have harsh side effects and cause changes to one's appearance (weight loss or gain, hair loss, skin changes, scarring etc.) which are distressing and can reduce confidence. Additionally, people are living with late effects from chemotherapy including nerve damage, fatigue, brain fog, bone pain, persistent blood clots, which can affect them for the rest of their lives. One person explained the worst aspect of chemotherapy was losing all her hair. She further explained it may 'sound silly' for others who haven't 'gone through what [she has] but it was devastating.' Current treatments have been described as 'savage' and 'not easy at all' by many, with one person expressing how a 6-month course of chemotherapy left him partially deaf in one ear. For various reasons, specific subsets of patients are not always suitable for the current standard of care offered on the NHS at the second line. One person informed us of how she and her consultant were unsure whether she was fit enough to undergo another dose of R-CHOP, given she was now older and frailer than when she was initially undergoing first line chemotherapy. Although eligible, stem cell transplants are not always a realistic option for many. We have consistently heard stem cell transplants being described as incredibly challenging – both to endure and to recover from. Patients often face uncertainty and fear about what the future holds. This was explained by one person who shared 'it's hard to know this is a disease that may keep coming back, especially when I am on trials, so the future is unknown.' Offering lisocabtagene maraleucel as an alternative option would be a great positive step forward. Carers find themselves devoting "everything" to caring for their sick, loved ones, constantly monitoring them for any changes and spend 'excruciating amounts of time' waiting through appointments and check-ups, fearing the worst. One carer explained how seeing their loved one experiencing 'really tough side effects' has been incredibly hard and knowing that the lymphoma can return is one of the worst aspects of this.

8. Is there an unmet need for patients with this condition?	There is a significant unmet need for effective and potentially curative treatments. In the absence of this, there is still a need for treatments with fewer long-term side effects which can also provide durable remissions, where traditional treatments have failed. Although treatment intent for LBCL may be curative, it does not always work for everyone. Due to this, those with lived experience express the unmet needs that exist within the NHS currently.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The biggest advantage identified by patients and carers is liso-cel's curative potential. This is significant especially for those facing limited, realistic treatment options with the current standard of care. Even if not curative for all, its ability to induce remission for a significant duration can greatly improve quality of life for both patients and their loved ones. This benefit is particularly favourable considering it is a one-time treatment. This means patients find liso-cel more convenient than the treatments available on the NHS as they can avoid multiple hospital visits and 'cycles upon cycles' of intensive chemotherapy regimens. This has positive knock-on effects on not only the burdens placed on them physically but also emotionally too. Our conversations with those in liso-cel-induced remissions highlighted an increased confidence that their current remission will last compared to previous ones. An individual we spoke to explained if she achieved remission with a stem cell transplant instead, she may have been 'more anxiously waiting for the ball to drop sooner than later.' Although the fear of her lymphoma returning is still present, she specified 'that's something I acknowledge may never go away.' Everyone we interviewed explained the positive impacts liso-cel has had on their quality of life. Some have returned to almost 'normality.' CAR-Ts in generally have been described as less burdensome by patients compared to current treatments. Additionally, unlike chemotherapy, the significance of patients' appearance remaining unchanged with CAR-T was highlighted several times in our conversations. Patients highlighted how they 'owe' their life to liso-cel and recognised their 'privilege' of having been the beneficiary of other people's experiences.' Whilst acknowledging the costs associated with CAR-T delivery, a 'short term hit of a higher costing may be a long-term saving over the alternative.' One person expressed 'I am no longer a burden on the NHS. No longer going through repetitive procedures.' With its ability to prolong the length, and improve quality of life and overall wellbeing, liso-cel can save resources required for the subsequent treatments that patients may otherwise have had to endure on the NHS.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients and their families can be anxious about the potential, serious side effects. The risks (however small) of cytokine release syndrome, neurotoxicity, and risk of admission to ICU are considered as disadvantages. However, they are manageable and a reversible risk in the majority. The drawback regarding accessibility and requirement to stay close to the hospital, even after treatment, was also highlighted by people we spoke to. Whilst it may not be a significant issue for some, this burden can be very heavy for others who face additional logistical and practical challenges, particularly if they do not have the support of carers. However, our conversations with wider CAR-T recipients highlighted that the requirement to stay within close proximity to the hospital also provided reassurance. The most shared sentiment amongst patients with lived experience of liso-cel and other similar CAR-T products was that the disadvantages and inconveniences of CAR-T are far outweighed by the benefits it provides. From a broader perspective, this will vary as people make their own risk-benefit calculations according to the different barriers and enablers they experience.

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?	As with other CAR-T treatments, there is a potential for short-lived inequalities in access to liso-cel. This is due to the reality that CAR-Ts are only administered in specialist CAR-T centres and also partly owed to the requirement to stay in close proximity to the centre post-infusion.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The aggressive nature of large B-cell lymphoma and the impact of its treatments can have significant effects on the mental and physical health and quality of life of both patients and their loved ones. • Patients with primary refractory and early relapsed large B-cell lymphoma face unmet needs brought about by the need for effective treatment options in the second line. • Lisocabtagene maraleucel provides an innovative option with a curative potential for those who otherwise face poorer outcomes with current available treatments. • The benefits of providing an effective and transformative one-time treatment, like liso-cel, as early as in the second line should not be overlooked. It means more people can benefit from improved access and can offer more patients an opportunity of a cure and better quality of life as a result. • Offering liso-cel at the second line could potentially spare many people from futile treatments and their associated toxicities whilst giving them their best chance at a cure earlier on in their treatment pathways.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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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.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees.

	The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Bristol-Myers Squibb £10,000
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with the types of non-Hodgkin lymphoma mentioned in this appraisal. We combined the information gathered from this, along with our experiences of working with these patients and their carers.

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?	Lymphoma is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type, with around 14,200 people diagnosed each year in the UK. There are many different types of NHL which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. In some cases, a slow growing low-grade lymphoma can transform into a faster growing high-grade type. Secondly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. B-cell lymphomas are much more common, accounting for 90% of cases. High grade B cell lymphomas can include: • Diffuse large B-cell lymphoma (DLBCL) • Primary mediastinal large B-cell lymphoma • Grade 3B follicular lymphoma • Other high-grade B-cell lymphomas These high-grade lymphomas can present in a number of different ways but most people first notice enlarging painless lumps, which are lymph nodes. These commonly are in the neck, groin or armpit. Due to the high-grade nature of these types of lymphoma the lymph nodes tend to enlarge very quickly. Sometimes the cancer can develop in other lymph nodes, or outside of the lymph nodes. This can cause a range of symptoms including cough and shortness of breath. A third of patients will also have B symptoms when they are diagnosed. These can be night sweats, weight loss, loss of appetite, itch and fatigue. Our patients often describe fatigue as being particularly debilitating and difficult to deal with. One patient said, *"fatigue affects all areas of life".* Very similar to fatigue, brain fog is something which patients with lymphoma often complain of. This makes people struggle to think and focus and can impact on work amongst other things. One patient described how it again can impact on all aspects of life.

	High grade B-cell lymphomas can affect people of various ages; DLBCL for example usually affects people aged over 65 whereas primary mediastinal large B-cell lymphoma typically affects people in their 20s and 30s. Therefore, the people affected may have spouses, children, or elderly parents to look after. These people are also impacted by the diagnosis of lymphoma. It can be mentally difficult as well as time consuming for these family members as they may have to transport their loved one to hospital appointments, collect medications, visit them in hospital or look after dependents on their own. It can also be a struggle for the family members to fully understand how their loved one is feeling. One patient we questioned described how her family found it, *"difficult to understand lymphoma, brain fog and fatigue".* They can often all end up feeling helpless, anxious, and alone. High grade B-cell lymphomas are treated with the aim of cure, however up to 45% of people become refractory to treatment, or relapse after treatment. The prognosis for these people is poor, and the current treatment regimens available only confer a median survival of twelve months. The psychological impact of a diagnosis of lymphoma is enormous. Patients have described insomnia, anxiety and a constant fear of dying to us. Being then told that you have relapsed, or that the treatment has not worked increases all of this further. Having refractory or relapsed disease brings about prolonged symptoms, further courses of treatment as well as an increased mental strain. People describe the worry of relapsing or not responding to treatment, and then if they do, the worry that there will not any further treatment options available. One patient described it as a constant worry that they would not get a cure for their DLBCL and said, *"Hard to put it to the back of one's mind, life is put on hold".* Another said, *"I lived in fear of recurrence".* The psychological impact of relapsed or refractory disease cannot be underestimated.

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 most common treatment for people with DLBCL and other high-grade B-cell lymphomas is a regimen of chemo-immunotherapy. This is usually a combination of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) or polatuzumab vedotin, rituximab, cyclophosphamide, hydroxydaunorubicin and prednisolone (Pola-R-CHP). Chemo-immunotherapy although often successful is very intense requiring multiple visits to the hospital. One patient described how she had to regularly travel to Oxford for her treatment which was disruptive to both her life and that of her loved ones, *"Difficult to travel to Oxford for SCT and daily chemo".* Chemo-immunotherapy also causes a number of short- and long-term side effects. Our patients have reported fatigue, sickness, diarrhoea, hair loss and recurrent infections due to neutropenia. These can all be incredibly debilitating. Long term side-effects can include prolonged fatigue and peripheral neuropathy. Younger patients may experience fertility issues which can be particularly distressing. If people do unfortunately relapse, or do not respond to treatment they require further treatment which is usually in the form of salvage chemotherapy and if well enough a stem cell transplant (SCT). This requires a long hospital stay away from friends and family. They can feel very isolated and have described their lives as being on hold during this time. The next treatment option would be CAR-T therapy with axicabtagene ciloleucel, or bispecific antibody therapies. These require people to be fit enough at this point, which after multiple treatments becomes less likely. Our patients are very complimentary and thankful for the treatment they have received but worry that options will run out, *"Very glad SCT and chemo are there as options but worry if need more treatments".*

8. Is there an unmet need for patients with this condition?	Patients feel that there are multiple treatment options available currently, but as people relapse or become refractory to treatment these treatment options run out. There is therefore an unmet need for these patients and having more options available would be hugely beneficial. *"As many treatment options are needed as possible to improve statistical chances of a cure".*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Our patients felt that having another treatment option available after the first relapse or treatment failure would be a huge advantage of this treatment. They felt that having to wait for multiple relapses made a chance of cure smaller, and also potentially caused more physical side effects and a prolonged mental impact. *"Very good to have more treatment options".* *"Difficult to know you have to wait to have 2 failed treatments before CAR-T".* Patients also feel that having a targeted treatment sounds better, simpler and more effective than most of the current treatment options.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The only disadvantages identified by our patients are the risk of cytokine release syndrome, and that it can only be given in certain treatment centres. This may mean that they have to have prolonged periods of time away from home. However, as it becomes more available to patients this may become less of a problem.

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?	Our patients could not identify any equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	*"The longer people have to wait for new treatments the more likely they are to die waiting".*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Relapsed or refractory high-grade B-cell lymphomas can be difficult to treat, with limited treatment options avalable. • Current treatment options have significant short- and long-term side effects. • The fear of not responding to treatment, and the knowledge that there are limited treatment options can have a huge psychological impact on patients. • Current treatment options can often require multiple, or prolonged trips to hospital which impacts carers and loved ones. •

Thank you for your time.

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Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 30 August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating relapsed or refractory large B-cell lymphomas and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Wendy Osborne
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) or follicular lymphoma grade 3B (FL3B)? ☐ A specialist in the clinical evidence base for relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B or the 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 ☐ Other (they did not submit one, I do not 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

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim for the treatment of relapsed or refractory diffuse large B cell lymphoma (RR DLBCL) is to attain a complete remission and for that remission to be sustained; the ultimate aim is to cure patients with RR DLBCL.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any reduction in lymphoma volume is significant but the most important is achieving a complete response as some of these will lead to cure. If a partial response is achieved, then this will usually lead to the patient living longer and having better symptom control but most people with a partial response eventually do go on an progress. A complete response in large cell lymphoma is important as a proportion of patients will be cured and those who achieve a CR usually have a longer duration of response compared to those in a partial response.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B?	Yes there is still an unmet need. For patients who relapse and are not given any further treatment then they would die in a short number of weeks to months.
11. How is relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	If a patient is auto fit and relapse within 12 months of first line polaRCHP then they will have Axi-cel 2nd line on the CDF. If they are auto fit and relapse after 12 months, then they will have 2nd line high dose chemo and an auto. If a patient cannot access 2nd line Axi-cel (either relapsed more than 12 months or not considered auto fit and the patients had to be autofit to enter the Zuma7 study) then they will often have 2nd line Rgemox (which is ineffective in most patients) so that they can then access Axi-cel 3rd line or they will be considered for glofitamab or epcoritamab (bispecific antibodies) or loncastuximab (antibody drug conjugate) and then palliative oral chemotherapy. Rituximab bendamustine polatuzumab is used less frequently now because we use polatuzumab first line (polaRCHP) and bendamustine depletes T cells and

	therefore we aim to avoid before using T cell engagers such as CAR T and bispecifics.
12. 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 what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	CAR T is currently already used as a standard of care in the NHS in both a second line and a 3rd line setting. No additional resource would be used and it would be a decision as to whether Axi-cel or Liso-cel is used 2nd line, it would not be both. This would be delivered in CAR T infusion centres which are already established.
13. 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? • Do you expect the technology to increase health-related quality of life more than current care?	Axi-cel is currently delivered in the second line setting and has a higher toxicity profile compared to liso-cel but Axi-cel is still on the CDF. The current standard of care in baseline commissioning is either high dose chemotherapy and an auto transplant or second line chemotherapy (eg Rgemox) and these have lower efficacy then lisocel. High dose therapy and an auto is associated with high toxicity and patients have to be in hospital for a month and it is only effective in about 20% of people/ Second line chemo such as Rgemox is less toxic but is not effective and most patients need to then have 3rd line treatment. I therefore would expect lisocel to increase length of life and quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Liso-cel would be more effective for older patients would would not be considered fit for high dose therapy and an auto transplant.

15. 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 example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Liso-cel will need to be delivered in a CAR T centre which is the case for current 2nd line Axi-cel, it is associated with less toxicity and so it will be easier to deliver. If comparing to baseline commissioned options then high dose chemo and an auto is delivered in an auto centre which may not be a CAR T centre and Rgemox would be delivered in all hospitals.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CAR T national panel discussion (NCCP) which is standard for all patients to ensure eligible as per pre-defined criteria.
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Time on treatment and time in hospital will be less with liso-cel compared to high dose chemo and an auto and there will also be a lower side effect profile with liso-cel/. Time on treatment will be less with lisocel compared to Rgemoox.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	CAR T is new technology which is enabling the patient's own immune system to have durable response against the lymphoma and this has been a step change approach over the last 5 years with a focus on T cell engagers.

19. 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 main side effects are CRS (cytokine release syndrome) which is easily managed with tocilizumab and ICANS (neurotoxicity) which is managed with steroids. Liso-cel has less CRS and ICANS than other CAR T products for lymphoma. Some patients have low blood counts after CAR T but this is often manageable with GCSF and usually recovers in a short number of weeks to months.
20. Do the clinical trials on the technology reflect current UK clinical practice? • 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? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The randomised trial was reflective of UK practice in that the standard arm was the UK standard of care of high dose chemotherapy and an auto transplant. The population across both arms was high risk and similar to a UK population in this relapsed setting. A significant improvement in EFS is clinically meaningful and the minimal toxicity seen was encouraging. The trial had crossover built in and therefore patients were apheresed across both arms and could move straight to liso-cel if high dose chemotherapy was ineffective. This was an optimal trial design for patients to ensure no delays in treatment and the trial design and crossover may account for EFS but not OS benefit.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance for axicabtagene ciloleucel [TA895]?	No
23. How do data on real-world experience compare with the trial data?	Similar outcomes
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	There is geographical inequality for CAR T. Although more centres are opening, patients who live a long distance from a centre are less likely to choose CAR T as a treatment option compared to those who live close by.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The study only included auto fit patients because they had to be randomised to possible auto and therefore older less fit patients would not be eligible and this is due to trial inclusion not because they would be unable to tolerate liso-cel.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Effective second line treatment option

Favourable toxicity profile

Real world data demonstrates similar efficacy to trial data

Less time in hospital, more options for ambulatory approach.

Would consider in older less fit patients

Thank you for your time.

Your privacy

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Part 1: Treating relapsed or refractory large B-cell lymphomas and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Christopher Fox
2. Name of organisation	University of Nottingham/Nottingham University Hospitals NHS Trust
3. Job title or position	Professor of Haematology/Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) or follicular lymphoma grade 3B (FL3B)? ☒ A specialist in the clinical evidence base for relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B or the 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 ☒ Other (they did not submit one, I do not 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

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
8. What is the main aim of treatment for relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Achieve durable complete remission and potentially cure
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Complete (metabolic) remission
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B?	yes
11. How is relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Pathway of care is reasonably well-defined and broadly consistent **Second-line** 1. For relapses <12months from completing first-line chemotherapy, patients who are fit for autologous stem cell transplant (ASCT) are offered axi-cel CD19 CAR T cell therapy 2. For relapses <12months from completing first-line chemotherapy, patients who are NOT fit for autologous stem cell transplant (ASCT) are offered further chemotherapy as 2L 3. For relapses >12months from completing first-line chemotherapy, patients who are fit for autologous stem cell transplant (ASCT) are offered ASCT

	Liso-cel as per submitted TA would be an additional option for group 1 with potential advantages over existing therapies particularly given lower rates of severe toxicity
12. 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 what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Liso-cel would be adopted and delivered within the current infrastructure established for other CD19 CAR T cell therapies – this would only be delivered at NHSE accredited CAR T delivery centres (specialist centres who also deliver allogeneic stem cell transplantation)
13. 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? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – the benefits for the intended patient group are clinically meaningful and is likely to extend life more than some treatments, whilst offering a lower toxicity profile (and therefore better HRQOL) than other existing treatments.
14. 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 have the relevant disease, treatment history and have sufficient medical fitness to tolerate CD19 CAR T cell therapy as 2nd line
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Lower rates of severe toxicity should make this therapy easier to deliver than existing therapies

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clear eligibility as set-out by NHSE and overseen by the National CART cell panel
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Likely to offer shorter period of time as a hospital inpatient
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – innovative and a step-change
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	A complex treatment with relevant side-effects but where effective has a substantial positive effect on long-term QoL and a reduction in future healthcare needs

20. Do the clinical trials on the technology reflect current UK clinical practice? • 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? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes reflective of UK practice EFS/PFS/CR/OS - yes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance for axicabtagene ciloleucel [TA895]?	Not for this indication
23. How do data on real-world experience compare with the trial data?	Comparable for CAR T cell therapy
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Not that I am aware of

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The patient population represents an area of unmet medical need

The technology is innovative and represents a step-change in therapeutic management

The technology offers a proportion of patients an opportunity for long-term remission of their lymphoma

The technology offers a clinically significant reduction in the risk of sever toxicities and a promising efficacy/toxicity profile compared to currently available therapies

Patients are likely to experience HRQoL benefits and there may be healthcare resource utilisation benefits for the NHS

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory large B-cell lymphomas or caring for a patient with relapsed or refractory large B-cell lymphomas. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 30 August**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with relapsed or refractory large B-cell lymphomas

Table 1 About you, relapsed or refractory large B-cell lymphomas, current treatments and equality

1. Your name	Christopher Bernard Strange
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory diffuse large B cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) or follicular lymphoma grade 3B (FL3B)? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Blood Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend the expert engagement teleconference.** ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B? **If you are a carer (for someone with relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B) please share your experience of caring for them**	After being diagnosed in February 2018 with stage 4 B DLBCL I received Chemotherapy (CHOP-R six cycles without R for last two cycles) and achieved a 15 months remission. It took two months of tests in December 2017 and January 2018 (numerous blood tests, scans, 2 bone marrow, 2 lung and one neck lymph node biopsies) before my condition was diagnosed and treatment started. I had dropped in weight from 12½ stones to 9 ½ stones from September 2017 to February 2018 and was extremely weak and feeble. My wife had to help me to wash and dress. I needed a walking frame to help me to get around my home for three months. I had previously been a fully able person. My wife has since told me that she did not think that I would leave hospital alive. When the condition returned, by which time I had regained half of the weight loss, I was extremely concerned for my future and that of my wife and family. The CHOP-R, whilst it had saved my life, had left me partially deaf in my left ear, a reduced sense of taste and smell, unable to do my pre-life activities (my wife and I have a smallholding with a flock of sheep, forestry, pastures and fences to maintain) and with digestion problems – heartburn, constipation and diarrhea. It also left me a more emotional person. I still get upset very easily at sad occasions that I witness. During my CHOP-R treatment and the following 15 months I had to watch my wife cope not only with my treatment and recovery but also cope with the running of our home and smallholding. It was running against my life plan to look after my wife and protect her from the heavy duties of our life. She, was at the end of 2021 74 years of age with her own health issues and I worried more about her than my ongoing

	issues. I was afraid that I would become a long-term burden on my family and possibly on the NHS and benefit system.
7a. What do you think of the current treatments and care available for relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a When my condition returned after 15 months remission my Consultant Hematologist had a long open and frank discussion with me regarding my options. She had with her the Macmillan Nursing Sister that had overseen my stays in hospital, tests and biopsies. They lead a formidable team of dedicated doctors, nurses and other carers who throughout my treatment keep me informed and abreast of what was happening to me and always available when I need help. I had total confidence therefore in her full disclosure of my options. She told me :- Option 1. I could refuse further treatment and let nature take its course. Option 2. More cycles of chemotherapy. This should result in a further state of remission but:- a. It is likely to be short term again resulting in more cycles of chemotherapy b. It is likely to leave me with side effects as had the earlier treatment c. As the years passed and my general health deteriorated (I was 74 years old by then) I would be less able to take the side effects. Option 3. CAR-T trial. My consultant knew of a trial being conducted at University College Hospital London. She explained that the new treatment looked promising and could result in long term remission. However, it was new treatment, may not be successful and my have side effects. If I undertook the trial and it failed, I could revert to Option 2. I asked to be referred and was, I shall ever be grateful, accepted.

	7b. During my cycles of CHOP-R I met many other patients receiving chemotherapy – mostly much younger that me. Some of these patients were on their second or third courses of treatment following periods of remission. I found mostly that the conversations that I had had left me dispirited for them realizing what desperate lives some of them were living. Job and career prospects damaged, marriage and family lives damaged, financial problems and despair in some that they were, or becoming, a burden to those close to them and a burden on the State instead of a contributor financially. Despite all of the wonderful care that they were receiving in the hospital their self-esteem, dignity and pride was diminishing as a result of their ongoing and repetitive condition. With this in mind Option 3 to question 7a became a “no brainer” to me.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The main disadvantages that I have seen are as much emotional as physical. The stress of biopsies is high. Blood tests and scans are stressful but undertaken for the greater good. For those going through courses of treatment year after year it must feel like the tide coming in and out relentlessly and wondering when it will stop. How can work life and family settle for them and for those close to them? Each course of treatment may bring a new and additional side effect.
9a. If there are advantages of lisocabtagene maraleucel over current treatments on the NHS please describe these. For example, the effect on your	9a Since my successful CAR-T treatment I feel almost reborn. I will be 78 years old in September and know that I should expect aches and pains at that age and not

quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does lisocabtagene maraleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	expect to do what I could when I was 25 but I am giving it a good try! I have regained all of my weight loss and most of my strength. I have resumed all physical work on my smallholding. Over the last three months I have laid over 100 sq metres of paving, shifting and laying paving slabs of 25 kg each. All of this is an example of a massive advantage of the results of the CAR-T treatment over the CHOP-R treatment. I have returned to normal family life. I am paying my way and no longer a burden on my family, friends, NHS or State Benefits etc. My quality of life has returned to what it would have been had cancer never entered my life. My self-esteem has now returned and I now feel that I am a contributor to society rather than a liability. This is all due to the wonderful CAR-T trial team and the treatment itself. When I laid in bed at UCLH receiving back my new fortified/modified blood cells I felt an overwhelming surge and a new will to live. For the first time in several years I felt that my own body was now fighting back and that it was cancer that was now in retreat. That feeling has never left me and I feel that my period of remission will now run to the end of what would have been my normal life without cancer. 9b Cure/long-term remission because with this achievable target all of the other advantages follow. 9c For me my CAR-T trial treatment has overcome all of the problems described in question 8 as I am now leading a normal life.

10. If there are disadvantages of lisocabtagene maraleucel over current treatments on the NHS please describe these. For example, are there any risks with lisocabtagene maraleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only disadvantage was that my CAR-T treatment could not be given at my local hospital. I was in UCLH for nearly 5 weeks without visitors due to distance of travel problems, ULEZ parking etc. but the trial team kept my family in touch whenever asked and I could use the telephone. Post hospital treatment was arranged by hospital car service but all in all I would have put up with far worse for the benefit of the treatment
11. Are there any groups of patients who might benefit more from lisocabtagene maraleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I am not able to answer this without guessing.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B and lisocabtagene maraleucel? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	I can only say for myself that I was given the treatment despite my old age.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I am sure that the committee will understand the financial implications better than me of a once and for all treatment against ongoing endless treatments. Also, from a National consideration, cured/long-term remission patients can return to work as tax payers, carers and contributors to society.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The less intrusive treatment offers cure/long-term remission
- The side effects are less problematic than those experienced with current treatments.
- Self-esteem returns to patients who now feel normal.
- Uncertainty of outcome of treatment is relieved to enable normal life planning to return.
- There is no barrier to age so nobody needs to feel on the scrap heap.

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External Assessment Group report: lisocabtagene-maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

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The authors have no competing interests to declare.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
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Executive Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (See section 1).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID3887	Summary of issue	Report sections
(1)	Generalisability concerns over the representativeness of TRANSFORM trial for NHS care.	2.6
(2)	Whether to use event-free survival (EFS) or progression free survival on subsequent therapy (PFS2) for economic modelling structure	3.2.2, 3.2.6
(3)	Choice of extrapolation for overall survival (OS)	3.2.6.3
(4)	Choice of extrapolation for time to next treatment (TTNT)	3.2.6.4
(5)	Utility value for "healthy" health state for first 5 years of model	3.2.7
(6)	Bridging therapy distribution	3.2.8.1.2
(7)	Subsequent therapy distribution	3.2.8.3
(8)	Adverse event costs	3.2.8.5

The key differences in QALY estimates between the company's preferred assumptions and the EAG's preferred assumptions are the modelling of OS and EFS/PFS2. The key differences in cost estimates are the distribution of subsequent therapies and adverse events modelled.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival and event-free/progression-free survival.

Overall, the technology is modelled to affect costs by:

- The cost of 2L and subsequent treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- The modelling of overall survival
- The modelling of adverse event costs
- The modelling of subsequent therapies received

1.3 *The decision problem: summary of the EAG's key issues*

The EAG had no key issues relating to the decision problem

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1: Generalisability of the TRANSFORM trial to NHS practice

Report section	2.6
Description of issue and why the EAG has identified it as important	People in TRANSFORM received different previous and subsequent therapies compared to NHS care and they received CAR T treatment more rapidly at 2L and 3L meaning very little dropout between liso-cel leukapheresis and infusion.
What alternative approach has the EAG suggested?	The EAG is unable to fully account for these problems, however they are considered individually in the other key issues.
What is the expected effect on the cost-effectiveness estimates?	It is unclear whether the relative efficacy of liso-cel is over or underestimated.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on real-world use of liso-cel at second line, on the impact of prior polatuzumab and the efficacy of subsequent recently approved therapies.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 2: Whether to use event-free survival (EFS) or progression free survival on subsequent therapy (PFS2) for economic modelling structure

Report section	3.2.2, 3.2.6
Description of issue and why the EAG has identified it as important	The company uses event-free survival to inform the economic model, however this pools together people who are cured and not cured at third line, introducing bias in favour of liso-cel.
What alternative approach has the EAG suggested?	The EAG prefers to use PFS2 to inform model health states, where people experiencing a PFS2 event are unlikely to be cured, meaning your health states are more homogenous. The EAG prefers a Weibull and log-logistic distribution for liso-cel and SOC respectively.
What is the expected effect on the cost-effectiveness estimates?	Impact of this change alone appears small but it is linked to other model changes.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 3: Choice of extrapolation for overall survival (OS)

Report section	3.2.6.3
Description of issue and why the EAG has identified it as important	The EAG considers the TRANSFORM data to be too immature to provide reliable estimates of cure proportions, as they are inconsistent with follow-up from the ZUMA-7 trial.
What alternative approach has the EAG suggested?	The EAG uses an alternative approach to obtaining OS extrapolations which are consistent with ZUMA-7 and PFS2
What is the expected effect on the cost-effectiveness estimates?	These changes reduces the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	Real-world follow-up of second line liso-cel use would inform the plausibility of current extrapolations.

Issue 4: Choice of extrapolation for time to next treatment (TTNT)

Report section	3.2.6.4
Description of issue and why the EAG has identified it as important	The company's modelling of EFS and TTNT resulted in differing cure proportions. The EAG was unclear why these outcomes would disagree.
What alternative approach has the EAG suggested?	The EAG prefers to use an EFS extrapolation to model TTNT, as it considers the data more mature.
What is the expected effect on the cost-effectiveness estimates?	This change alone increases the cost-effectiveness of liso-cel, however it is also affected by other assumptions of subsequent therapy use.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up from the trial may provide more reliable estimates of TTNT.

Issue 5: Utility value for "healthy" health state for first 5 years of model

Report section	3.2.7
Description of issue and why the EAG has identified it as important	The utility value used by the company comes from TRANSFORM however is high compared to other sources for a similar population.
What alternative approach has the EAG suggested?	The EAG prefers to use a utility value from TA895 for this health state for consistency with other appraisal, and plausibility of value.
What is the expected effect on the cost-effectiveness estimates?	This decreases the QALY gains associated with liso-cel.
What additional evidence or analyses might help to resolve this key issue?	Alternative sources of data may provide additional information on the most appropriate utility value for this health state.

Issue 6: Bridging therapy distribution

Report section	3.2.8.1.2
Description of issue and why the EAG has identified it as important	The company use information from the liso-cel arm of TRANSFORM to inform the proportion of people receiving bridging therapy and the distribution of bridging therapies used to inform their modelling for second and third line CAR T therapy.
What alternative approach has the EAG suggested?	The EAG prefers to use UK specific data to model proportion receiving bridging therapy and the distribution of bridging therapies used prior to CAR T infusion
What is the expected effect on the cost-effectiveness estimates?	Changing to the EAG preferred assumption worsens the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	The availability of line-specific bridging therapy information could further improve the modelling assumptions.

Issue 7: Subsequent therapy distribution

Report section	3.2.8.3
Description of issue and why the EAG has identified it as important	The company use data from TRANSFORM to model the distributions of subsequent therapies, however this does not appear representative of UK NHS care. In particular the high rate of subsequent CAR T in the SOC arm.
What alternative approach has the EAG suggested?	The EAG prefers estimates specific to UK care provided by the company's clinical experts for the distribution of the types of subsequent therapies received, and use information from NHS England to inform use of novel therapies.
What is the expected effect on the cost-effectiveness estimates?	This is the most influential change and liso-cel no longer dominates SOC. Instead liso-cel is more expensive but provides more QALYs, meaning the ICER can be considered.
What additional evidence or analyses might help to resolve this key issue?	Data collection from real-world CAR T use may further enhance the modelling.

Issue 8: Adverse event costs

Report section	3.2.8.5
Description of issue and why the EAG has identified it as important	The company apply the CAR T tariff cost to account for the costs of adverse events in the liso-cel arm which excludes AEs occurring 100 days beyond therapy (i.e. those associated with subsequent therapy), but for SOC they apply the costs of events that occurred in TRANSFORM and also the CAR T tariff cost, potentially double counting.
What alternative approach has the EAG suggested?	The EAG attempts to remove the portion of the tariff cost attributable to AEs when it is applied to third line CAR T, for consistency with the approach for liso-cel.
What is the expected effect on the cost-effectiveness estimates?	Changing to the EAG preferred assumption worsens the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	A breakdown of adverse events by line of therapy would allow for more detailed modelling of AE costs.

1.6 *Other key issues: summary of the EAG's view*

The EAG did not identify any further key issues.

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

Table 2: Summary of EAG's preferred assumptions and ICER

Assumption	ICER(£/QALY)
Company base case	-£29,314 (SOC dominated)
EAG01: Use PFS2 for model health state occupation	-£30,589 (SOC dominated)
EAG02: Weibull distribution used for liso-cel PFS2 and Loglogistic distribution used for SOC PFS-2	-£30,961 (SOC dominated)
EAG03: Discount applied per cycle.	-£27,986 (SOC dominated)
EAG04: log-logistic parameters re-estimated and used for liso-cel & SOC OS	-£23,149 (SOC dominated)
EAG05: log-normal and generalised gamma parameters re-estimated and used for liso-cel and SOC TTNT respectively	-£36,540 (SOC dominated)
EAG06: Bridging therapy changed	-£27,656 (SOC dominated)
EAG07: AE costs removed for 3L CAR T	-£24,130 (SOC dominated)
EAG08: Subsequent therapy changed including proportion in SOC receiving CAR T at 3L	£38,126
EAG09: Utility changed for pre-PFS-2 state	-£26,078 (SOC dominated)
EAG10: Starting age of model changed	-£31,806 (SOC dominated)
Cumulative	£38,638

Table of Acronyms

Acronym	Definition
1L	First-line
2L	Second-line
3L(+)	Third-line (plus)
ABC	Activated B-cell like
ACM	Appraisal committee meeting
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogenic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
Axi-cel	Axicabtagene ciloleucel
BCMA	B-cell maturation antigen
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criterion
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medical Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	Cyclophosphamide, doxorubicin and prednisone
CI	Confidence interval
CII	Cost Inflation Index
CNS	Central Nervous System
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CRR	Complete response rate
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
CUA	Cost utility analysis
DCO	Data cut off
DHAP	Dexamethasone, cytarabine, cisplatin
DHAX	Dexamethasone, cytarabine and oxaliplatin
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Event-free
EFS	Event-free survival
EMA	European Medicines Agency
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study

Acronym	Definition
ESHAP	Etoposide, methylprednisolone, high dose cytarabine and cisplatin
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FISH	Fluorescence in situ hybridisation
FLBCL	Follicular large B-cell lymphoma
GCB	Germinal centre B-cell
GDP	Gemcitabine, dexamethasone and cisplatin
GEMOX	Gemcitabine and oxaliplatin
GP	General practitioner
HCRU	Healthcare resource use
HDCT	High dose chemotherapy
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HMRN	Haematology Malignancy Research Network
HR	Hazard ratio
HRQOL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
HTA	Health Technology Assessment
ICE	Ifosfamide, carboplatin and etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IHC	Immunohistochemistry
INHB	Incremental net health benefit
IPD	Individual patient data
IPI	International Prognostic Index
IRC	Independent review committee
IRR	Infusion Related Reaction
IRT	Interactive Response Technology
ITT	Intention to treat
IVE	Ifosfamide, etoposide and epirubicin
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
LFT	Liver function test
Liso-cel	Lisocabtagene maraleucel
LVEF	Left ventricular ejection fraction
LYG	Life years gained
LYM	Lymphoma
MAIC	Matching adjusted indirect comparison
MAS	Macrophage activation syndrome
MCM	Mixture cure model
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimal Important Difference
MUGA	Multi-gated acquisition scan
MYC	Myelocytomatosis oncogene
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NEC	Not elsewhere classified
NHB	Net health benefit
NHL	Non Hodgkin’s lymphoma
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified

Acronym	Definition
NR	Not reported
ONS	Office for National Statistics
ORR	Overall Response Rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PICO	Population, Intervention, Comparators, Outcomes
PMBCL	Primary Mediastinal B-cell lymphoma
Pola	Polatuzumab
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QOL	Quality of life
R-	Rituximab
RCT	Randomised controlled trial
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SAS	Safety analysis set
SCT	Stem cell transplantation
SD	Stable disease / standard deviation
SE	Standard error
SLE	Systemic lupus erythematous
SLR	Systemic literature review
SMR	Standardised mortality ratio
SOC	Standard of care
STM	State transition model
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
tFL	Transformed follicular lymphoma
THRBCL	T-cell histiocyte rich large B-cell lymphoma
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor
TSD	Technical Support Document
TTNT	Time to next treatment
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

The EAG has reviewed the company submission (CS) from Bristol Myers Squibb (BMS) to NICE on the clinical effectiveness and cost-effectiveness of lisocabtagene maraleucel (liso-cel) for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) or follicular lymphoma grade 3B (FL3B) after first-line chemotherapy in people who are eligible for stem cell transplantation.

Liso-cel is currently licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy but the NICE appraisal of liso-cel in this indication was suspended in November 2021.
The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of approval for liso-cel in April 2023. A marketing authorisation type II Variation extension application to the MHRA was made in December 2023 for the treatment of [redacted].

1.2 *Background*

The company provides a description of liso-cel and of the relevant health condition in sections 1.2 and 1.3 of the company submission (CS). This section provides a critique of the company overview of the disease, the technology, and the positioning of lisocabtagene maraleucel (liso-cel) in the treatment pathway.

1.2.1 Condition, epidemiology and symptoms

The CS cited relevant references in their description of the health condition (B.1.3.1), although the EAG noted that some of the citations were secondary references (e.g. Tilly 2015,[1]) rather than primary studies. Non-Hodgkin lymphoma (NHL) is one of the

most common types of cancer. In England, 10,710 people were diagnosed with NHL in 2020, with an age standardised incidence of 19.7 per 100,000 population.[2] NHL is categorised according to the type of white blood cell affected, B cell or T cell.

Large B-cell lymphomas (LBCL) are one of 12 families of mature B-cell neoplasms. The CS accurately cites HMRN data, estimating that 5,440 people are newly diagnosed with LBCLs each year in the UK, with an annual incidence of 8.3 cases per 100,000 people. LBCL has been classified by The World Health Organization (WHO) into several specific entities.[3, 4] The types that are of interest to the current submission are those that liso-cel is indicated for:

- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
- High-grade B-cell lymphoma (HGBCL)
- Primary mediastinal B-cell lymphoma (PMBCL)
- Follicular lymphoma grade 3B (FL3B)

Due to similarity in treatment pathway at second-line for these four aggressive subtypes of lymphoma, the CS collectively refers to them as LBCL. The EAG clinical experts agree that in clinical practice, DLBCL, PMBCL, HGBCL and FL3B are treated similarly.

In the UK, DLBCL is the most common type of LBCL, accounting for 40% of all NHL cases (approximately 4,870 cases, typically presenting in older adults and characterised by aggressive, heterogeneous clinical features).[5, 6] PMBCL, a rarer type, has an average annual incidence of 0.2 per 100,000 (140 cases per year), affects young adults and women predominantly, and is marked by fast-growing tumours in the mediastinal area.[7]. HGBCL encompasses aggressive lymphomas with specific genetic translocations, including double or triple-hit lymphomas which involve rearrangements of MYC and either BCL2 or BCL6 genes (or both).[8, 9] The CS states that data on HGBCL incidence are scarce but that it is generally considered a rare NHL subtype, citing a secondary reference suggesting it comprises 1–2% of cases.[10] The EAG was unable to verify the incidence data. The CS states HGBCL often presents in elderly patients with widespread disease and high prognostic scores, however the EAG is unable to access the citation to verify this. FL3B, now classified as FLBCL, is a rare subtype of follicular lymphoma.[11]

Follicular lymphoma has an average annual incidence of 3.6 per 100,000 people in the UK, amounting to approximately 2,320 cases per year.[7] The CS also states that FL3B accounts for only 5-10% of these cases and presents similarly to DLBCL, although the citations used by the company are not primary studies and the EAG is unable to verify the proportion of cases. The accuracy of these data has no implications for the results or conclusions of the CS.

Prognostic tools for LBCL involve scoring systems that assess clinical characteristics such as age, presence of B symptoms, performance status, lactate dehydrogenase levels, number of sites involved, and clinical stage.[12] These tools include:

- International Prognostic Index (IPI)
- Revised IPI (R-IPI)
- National Comprehensive Cancer Network-IPI (NCCN-IPI)
- Age-adjusted IPI (aaIPI)
- Secondary age-adjusted IPI (sAAIPI)

The sAAIPI, assessed in a study of patients with aggressive relapsed/refractory (R/R) DLBCL eligible for stem cell transplantation, effectively predicted progression-free survival (PFS) and overall survival (OS) by categorizing patients into low, intermediate, and high-risk groups.[12] According to the CORAL study, the sAAIPI, together with early relapse and prior rituximab exposure, was negatively correlated with the response to second-line treatment and overall survival (OS).[13]

Patients with LBCLs typically present with painless swellings in the neck, armpit or groin caused by enlarged lymph nodes, accompanied by general symptoms (B symptoms) such as fever, night sweats, and significant weight loss.[6] These symptoms significantly impair the health-related quality of life (HRQoL) of patients, as shown by reduced scores across all domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) compared with an age- and sex-matched reference cohort of the general population in a Dutch study using population-based registry data of patients with DLBCL.[14] The current second-line standard of care (2L SOC) involving high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (SCT) further diminishes HRQoL.[15] Severe short- and long-term side effects, such as infections,

cardiac toxicity and secondary tumours are a risk of SCT.[16, 17] Patients undergoing HDCT and SCT have notably poorer physical and mental HRQoL for a median of eight years post-treatment compared with age- and sex-matched controls.[18] The emotional toll is especially high for those with relapsed/refractory (R/R) disease,[19] who experience even greater reductions in HRQoL with subsequent treatment lines.[20] The CS states there is an unmet need for new second-line (2L) treatments to improve patient outcomes and prevent disease progression.

1.2.2 Position of liso-cel in the clinical pathway

First line

The UK treatment pathway for LBLC is outlined in CS Figure 4. First line standard of care for LBCL in UK practice is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) which the company states was used in around 80% of DLBCL patients in 2015. The company cites the National Comprehensive Cancer Network (NCCN) guideline,[21] which the EAG has not been unable to access, however clinical advice to the EAG confirms that this is the most commonly used first-line therapy. There has been some change in first line practice with the 2023 NICE recommendation of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola+R-CHP) for DLBCL. The company reports that their clinical advisors state that most [DLBCL] patients receive Pola+R-CHP, however clinical advice to the EAG is that this isn't necessarily the case for all patients.

CS Figure 3 reports cure rates with first-line treatments to be 60-70% in 2021 and estimates the cure rate in the Pola+R-CHP era to be around 70-80% (although the EAG notes that the company cites a secondary reference and the original data may actually relate to 2014). The EAG clinical advisers agree with these estimates, therefore there are no implications for the results or conclusions of the CS.

Second line

The company focus is on second line treatment for people with R/R LBCL who are eligible for SCT. The CS reports that approximately 50% of people with R/R LBCL are eligible for SCT. The CS only uses secondary sources for these estimates and the EAG hasn't verified the primary sources, however the EAG clinical experts agree 50% is reasonable. The second line treatment pathway for these people is discussed

in CS Section B.1.3.4. The current standard of care (SOC) for SCT eligible people is re-induction therapy with platinum-based immunochemotherapy followed by high dose chemotherapy and SCT in responding people. The choice of reinduction immunochemotherapy varies. The CS reports that their clinical experts most commonly use rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP) and rituximab, ifosfamide, carboplatin and etoposide (R-ICE). The CS report that around half of those eligible for SCT in principle will go on to receive it and of those who do receive it approximately half again experience further relapse. This is outlined in a hypothetical sample in CS Figure 3. The EAG were unable to verify these data in all of the literature cited, for example in Sarkozy 2018[22] the proportion of SCT-eligible patients who received SCT was 40%. However, the EAG clinical adviser concurred that the proportions in CS Figure 3 were reasonable.

Although not currently routine clinical practice, clinical advice to the EAG is that all people who are R/R within 12 months and eligible for SCT receive axi-cel via the Cancer Drugs Fund.

For those not eligible for SCT, CS Section B.1.3.2 reports that for these patients there is no established SOC and treatment can be palliative. Clinical advice to the EAG is that in UK practice these patients will often have another line of salvage chemotherapy. While this is not usually curative, if they relapse or do not respond some may then have 3rd line CAR T therapy without having SCT.

The CS summarises the UK treatment pathway in Figure 4. The anticipated positioning of liso-cel is shown at second-line for those with R/R disease and eligible for SCT.

Third line

Subsequent treatments for those relapsing after current SOC at second line are outlined in CS Section B.1.3.4 and presented in CS Figure 4. The third-line treatment landscape is evolving and the EAG clinical adviser confirmed that the various options for third-line treatment within current SOC are described in the CS, also noting that most people receive CAR T following second line SOC if fit enough. This concurs with the CS experts who estimated between 40-85% would receive axi-

cel. The CS clinical experts anticipated third line treatments following treatment with liso-cel would be bispecific antibodies, mostly glofitamab or epcoritamab. The CS reports the proportions estimated to receive each of these to be 37.5% (range 25-40%), the EAG believes this is a typographical error as CS reference 45 reports rates of 32.5% (which is also used in the health economic model, see CS Table 78).

Overall, the EAG are satisfied that the clinical pathway presented in the CS generally reflects current UK practice.

Unmet need

CS Section B.1.3.5 states that current SOC for those with early R/R LBCL and eligible for SCT is associated with limited survival benefit because, as discussed above, approximately half of people don't receive SCT and half who do experience a further relapse. The CS provides data on event free survival (EFS) rates from SOC arms of three RCTs of second-line treatments, including the pivotal RCT for liso-cel included in the present submission.[23] These rates for EFS were also summarised in CS Table 5, where the EAG notes that only two of the three RCTS reported median EFS. Therefore, the EFS cited for SOC ([redacted] or less) was actually based on two trials, one of which was the liso-cel trial included in the submission. The EAG notes that EFS was 3.0 months in the SOC arm of the BELINDA trial.[24] Although there are a range of factors to consider in these estimates, they appear reasonable to the EAG clinical advisers.

The CS also describes that people who receive SCT as current SOC may experience both short term toxicity during the treatment phases but also longer-term adverse effects which can have a negative impact on quality of life. The EAG clinical advisers note that there can be significant effects on quality of life as a person starts second-line treatment, however this is irrespective of the type of treatment. On checking the citations provided by the CS[15-18, 20] the EAG generally concurs that the evidence provided supports the claim of adverse events and quality of life effects from SCT, but notes that these data were not specific to SCT at second-line treatment for R/R LBCL.

The CS makes their case that liso-cel can address the current unmet need of people with R/R LBCL from meaningful improvements in clinical outcomes and a favourable safety profile, summarising key results from the TRANSFORM trial, the pivotal trial for the appraisal, which is summarised in Section 2.2 below.

1.3 *Critique of company's definition of decision problem*

The EAG's comments on the company's decision problem can be seen in Table 3. There are some differences between the company decision problem and the final NICE scope but the EAG has no major concerns. The evidence provided in the submission for liso-cel is aligned with the decision problem population.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with relapsed or refractory aggressive B-refractory DLBCL, HGBCL, PMBCL or FL3B after 1 prior therapy	Adults with early (≤ 12 months) relapsed/primary refractory DLBCL, PMBCL, HGBCL or FL3B who are eligible for SCT	The population included in the final scope is broader than the TRANSFORM trial in the following two aspects: • Only patients with early relapsed (within 12 months)/primary refractory disease are included in TRANSFORM, in line with license for liso-cel • Only patients eligible for SCT enrolled in the TRANSFORM trial The population considered for this submission is therefore narrower than the NICE final scope. This represents a subpopulation of the anticipated licensed indication in order to align with the population included in the pivotal TRANSFORM trial, which enrolled only patients who were eligible for SCT and had early relapsed/primary refractory disease. Liso-cel is also being evaluated for the treatment of relapsed or refractory (R/R) LBCL patients	The EAG agrees that this narrower population represents a subgroup of the relevant patient population and that the clinical evidence in the TRANSFORM trial matches the population in the decision problem. There is no uniform definition for eligibility for SCT and the EAG clinical advisers confirm that this can vary across the UK. At clarification it was confirmed to the EAG that the TRANSFORM trial did not include any specific definition regarding eligibility for SCT (see Section 2.2.2 for further discussion).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			who are ineligible for HDCT and ASCT (SCT-ineligible) in the Phase II trial TRANSCEND-PILOT (NCT03483103).[25] This population is not included in this submission and will be appraised separately, in order to align this submission with the population included in the TRANSFORM trial and licence for liso-cel in this indication.	
Intervention	Lisocabtagene maraleucel	Lisocabtagene maraleucel	In line with the NICE final scope.	The EAG agrees that the intervention is in line with the NICE scope. Liso-cel is currently indicated for the treatments of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy and a marketing authorisation type II Variation extension application to the MHRA for a license in Great Britain was made in December 2023. Liso-cel is anticipated to be indicated for the treatment of: • [redacted]
Comparator(s)	Established clinical management without	SOC re-induction therapy (R-DHAP [rituximab,	There are several re-induction therapies available in the UK. In	Although advice to the EAG is that SOC regimens are generally

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	lisocabtagene maraleucel, including but not limited to: • Immunotherapy with HDCT with or without ASCT Polatuzumab vedotin with rituximab and bendamustine (Pola+BR; if haematopoietic stem cell transplant is not suitable)	dexamethasone, cytarabine, cisplatin], R-ICE [rituximab, ifosfamide, carboplatin, etoposide], R-GDP [rituximab, gemcitabine, dexamethasone, cisplatin]) followed by HDCT and ASCT in responders	this appraisal, only R-DHAP, R-ICE and R-GDP are considered as relevant comparators, as these regimens are deemed the most routinely or commonly used in UK clinical practice, according to feedback received from UK clinical experts. Additionally, as the population for this submission is patients who are eligible for SCT, Pola+BR is not considered a relevant comparator as it is licensed for those who are not suitable for ASCT (TA649).	centre-specific and the use of R-DHAP is low, the EAG agrees that the SOC regimens included in the comparator are those most commonly used in UK clinical practice, and that SOC is the appropriate comparison for the restricted population (those eligible for SCT) in the company decision problem.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • event-free survival • response rates • adverse effects of treatment • health-related quality of life	All outcomes specified in the NICE final scope are included in the submission as follows: • event-free survival (time from randomisation to death from any cause, progression, failure to achieve complete response or partial response by 9 weeks post-randomisation or start of new antineoplastic therapy	Event-free survival (EFS) is the primary endpoint from the TRANSFORM trial.[26] For early relapsed/primary refractory LBCL, this endpoint is more clinically relevant than progression-free survival (PFS) given the curative intent of treatment. In this indication, 'stable disease' is not considered a successful treatment outcome and, therefore, patients who remain progression-free but with stable disease are moved on to receive a subsequent treatment line. In TRANSFORM, these	The EAG agrees that the outcomes presented reflect those in the NICE final scope. Clinical expert advice to the EAG is that there is no standard definition of EFS and that EFS is not a validated end-point in clinical trials, but that the rationale for the definition used in the TRANSFORM trial is reasonable. The EAG clinical advisers also agreed that EFS is a more appropriate outcome than PFS, agreeing that stable disease is not considered a successful outcome.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		due to efficacy concerns, whichever occurs first) • overall survival (time from randomisation to time of death due to any cause) • progression-free survival (time from randomisation to progression, or death from any cause, whichever occurs first) • progression-free survival on next line of therapy (time between randomisation to progressive disease on the next line of subsequent treatment or death from any cause) • response to treatment, including: ○ complete response rate (percentage of patients achieving a complete response) ○ duration of response (time from first response to disease progression,	patients could crossover into the liso-cel arm and, as a result, any comparison of progression-free survival between liso-cel and standard of care is likely to be biased. In line with the approach taken in TA895, EFS will therefore be used alongside overall survival (OS) and health-related quality of life (HRQoL) data to capture the most important health related benefits of liso-cel in the cost-effectiveness modelling.[27]	The EAG considers that the additional, non-scoped outcome of progression-free survival on next line of therapy (PFS2) is important. This outcome includes the impact of subsequent therapies received and the EAG argues that as people receive potentially curative therapies at third line, PFS2 may be a better outcome from which to derive health states for the cost-effectiveness modelling. This is discussed in more detail in Section 3.2.6.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		start of new antineoplastic therapy due to efficacy concerns or death from any cause) ○ overall response rate (percentage of patients achieving an objective response of partial response or better) • adverse effects of treatment health-related quality of life using the global health/quality of life, fatigue, physical and cognitive functioning subscales of the EORTC QLQ-C30, the FACT-LymS and EQ-5D		
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. The reference case stipulates that the time horizon for estimating clinical and cost	• The cost-effectiveness of liso-cel versus SOC has been evaluated, in line with the NICE reference case • A lifetime horizon has been adopted within the analysis to sufficiently reflect any differences in costs between the	In line with the NICE final scope	The EAG agrees that the cost-effectiveness of liso-cel addressed in the CS has been evaluated in line with the NICE reference case and is appropriate for this appraisal.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	technologies being compared • Costs were considered from an NHS and Personal and Social Services perspective (PSS) A patient access scheme (PAS) for liso-cel was included in the analysis		

ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; EFS: Event-free survival; FL3B: follicular lymphoma grade 3B; HDCT: High-dose chemotherapy; HGBCL: high grade B-cell lymphoma; HRQoL: health-related quality of life; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; R/R: relapsed/ refractory; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; SOC: Standard of Care; SCT: stem cell transplant.

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The EAG reviewed the methods used by the company to assess the eligibility criteria, identify, extract, assess risk of bias and synthesise the evidence on the safety and efficacy of treatment for patients who are SCT-eligible with R/R LBCL receiving 2L treatment. A range of study types from RCTs to observational studies were included. The review initially included various global therapies; this was then refined to focus on the NICE decision problem as discussed further below.

2.1.1 Searches

The searches were conducted in October 2017 and updated and re-ran six times, most recently in February 2024. The original Medline and Embase searches were searched via the ProQuest platform, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid and the Database of Abstracts of Reviews of Effects (DARE) were searched via the Centre for Reviews and Dissemination (CRD) database (CS Appendix D.1.1.1 Table 10). Conference proceedings were searched across eight conference websites in March 2023 and February 2024. Six conference websites (with the addition of the European Organisation for Research and Treatment of Cancer (EORTC) and the International Workshop on non-Hodgkin Lymphoma (iwNHL) in the March 2023 and February 2024 SLR update were searched in April 2019 and October 2017 (CS Appendix D.1.1.2 Table 12, Table 13 and Table 14). Three clinical trials registries were searched in March and December 2023. The search terms are provided but the numbers of results and included studies are not reported. The numbers of search results reported in the PRISMA flow diagrams from the 'Identification of new studies via other methods' indicates broad searches were carried out (CS Appendix D.2 Figure 1 and Figures 2-6 supplied in the CS Clarification response). It is also not reported if a date limit was applied to these searches. Not applying a date limit to the search carried out in March 2023 would be optimal, as the registers were not reported to have been searched in April 2019 or October 2017 (CS Appendix D.1.1.2 Table 14 and Figure 6: Combined PRISMA diagram for the October 2017 clinical SLR, including subsequent update in 2019).

Systematic reviews were sought from additional database searches and the bibliographies of included studies were hand-searched to identify further reports (CS Appendix D.1.1 Hand searches). Search terms for the concepts related to refractory disease are omitted, such as drug resistance, salvage therapy or treatment failure. The Medline, Embase and Cochrane Library searches contain a restricted amount of exploded indexing terms (MeSH and Emtree), which would result in the narrower indexing terms not being searched, thus limiting the sensitivity. The Medline (MeSH) and Embase (EMTREE) indexing terms for study types contains mainly EMTREE terms and a large proportion of MeSH terms are not included in the search. The free-text search terms contain limited and inconsistent use of truncation and adjacency operators. The free text searches were also not searched in fields beyond the Title or Abstract. Searching in the 'Keywords/identifiers (IF)', 'Subjects (SU)' or 'Anywhere except full text (NOFT)' fields would have increased the comprehensiveness of the search (CS Appendix D.1.1.1 Electronic database search terms - Table 9: Search terms used for database searches (Embase, Medline) (via ProQuest) – April 2019 and October 2017 SLRs combined).

The update searches from July 2020 onwards are significantly more comprehensive and well-constructed (CS Appendix D.1.1.1 Tables 8-1). The searches contain database-specific indexing and free-text terms, including keywords. However, the search was only run for records added to databases from April 2019 onwards. The EAG believe that the update search should not have been limited to this date, given the major changes that were applied; therefore, the search is not a true update of the original and potentially eligible studies published prior to 2019 may have been missed. The update search focusses on the population/ condition (R/R DLBCL) and study type only. Not including terms for the intervention increases the sensitivity of the searches. Language or publication format limits were not applied. The search field 'Publication type' (.pt) was not included in the search lines for study type for randomized controlled trials, clinical trials or observational studies from the Medline search study type filters (CS Appendix D.1.1.1 Tables 1, 2, 3, 5 and 7 lines 12-16), which may have resulted in a small number of studies being missed.

The search terms used for searching the grey literature and conference sources are provided but the numbers of retrieved and included results are not (CS Appendix D.1.1.2 Tables 12, 13 and 14). Full details of the reviews, guidelines and grey

literature examined in the hand-searches are also not reported (CS Appendix D.2 Search results). Only conference proceedings from 2016 onwards were searched. A search of older conference proceedings may have identified further trials that were never published, to counter publication bias.

The EAG had some concerns about the reporting of the search figures, due to discrepancies in numbers of results reported in the search strategy and the PRISMA diagrams provided in the company clarification response. For example, there are 464 Medline results reported in the search strategy in Appendix Table 2 and 506 in the PRISMA flow diagram (Figure 2 CS Clarification response A24).

124 articles were included in the updated searches and reported in the CS appendix. The EAG note some discrepancies in the reasons for exclusions in the CS appendix. The company clarified (clarification question A5) that, the reasons for exclusion were 'incomplete' or 'insufficient data' when they lacked clear information on prior lines of treatment, had unknown treatment lines, mixed treatment lines without subgroup data, mixed histologies without subgroup data, or combined both mixed treatment lines and histologies. Additionally, studies were excluded for 'other' reasons such as having few eligible patients, being protocols with no results, or not being relevant to the topic of the SLR. The EAG consider that the reasons provided are reasonable. The CS only included one article as being relevant for the decision problem.

2.1.2 ROBIS Assessment of company SLR

A summary of the EAG's quality assessment of the company's systematic literature review (SLR) using the ROBIS tool is presented in Appendix 1. The EAG has some concern over the risk of bias. There is concern regarding the original search strategy and restrictive update searches and also issues over the application of the screening against the eligibility criteria. The EAG checked all included and excluded studies and found that these were all in line with the eligibility criteria, however, there was some disagreement on the reasons for exclusion. Only one study originally identified by the SLR was eventually included in the CS but the criteria used to assess eligibility of the other studies were not explicit. The EAG consider that it was

appropriate that no indirect comparison was conducted as the CS only included one head-to-head comparison to inform the clinical evidence.

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

2.2.1 Overview

The source of evidence for the assessment of clinical effectiveness of liso-cel for people with LBCL who have relapsed within 12 months or are refractory to first line immunochemotherapy, and are eligible for ASCT, is from a single RCT, the TRANSFORM trial (NCT03575351). The CS presents data from the final data-cut off (DCO) dated October 2023, with a clinical study report (CSR) from an earlier DCO (May 2022) also provided in the company's reference pack. The main publication for TRANSFORM, Abramson 2023,[26] reports the DCO of May 2022 for the primary analysis. Further details of the planned interim analyses of TRANSFORM are given in CS section B.2.6.1.

TRANSFORM is an open-label parallel-group Phase III multinational RCT conducted in 11 countries across Europe and the USA, comparing liso-cel with SOC. A summary of the trial design is presented in CS Figure 5, and a summary of TRANSFORM methodology with cross-references to the relevant sections in the CS where more detail can be found is presented in Table 4. Further description is below.

Table 4: Summary of TRANSFORM methodology

Method step	Summary details	Section(s) of CS of relevance or other source
Method of randomisation	Permuted-blocks method with a dynamic block size.[a] Stratified by response to first line (1L) therapy	B.2.3.1

	(refractory versus relapse)[b] and sAAIPI (0–1 versus 2–3). Interactive response technology.	

Eligibility criteria	• Aged 18–75 years
	• Eligible for ASCT
	• LBCL:
	  ○ DLBCL not otherwise specified (NOS), de novo or transformed from indolent NHL
	  ○ HGBCL with rearrangements of MYC and either BCL2, BCL6, or both with DLBCL histology
	  ○ PMBCL
	  ○ T-cell histiocyte rich LBCL (THRBCL)
	  ○ FL3B
	• Refractory disease (SD, PD, PR or CR with relapse ≤ 3 months) or relapsed disease (CR with relapse ≤ 12 months), to CD20 antibody and anthracycline containing first-line therapy
	• ECOG performance status of 1 or less
	• Adequate organ function (definitions provided)
	• PET-positive disease as per Lugano 2014 criteria[28]
		B.2.3.1, Table 7

Trial drugs by period of study	Liso-cel arm: bridging therapy if needed (R-DHAP, R-ICE or R-GDP), followed by lymphodepleting chemotherapy and liso-cel. SOC arm: three cycles of re-induction therapy (R-DHAP, R-ICE or R-GDP) followed by HDCT and ASCT in those responding. Participants meeting specific criteria could crossover to liso-cel.	B.2.3.1, Table 7

Primary endpoints of relevance to the decision problem	Event free survival (EFS), defined as time from randomisation to progression, failure to achieve CR or PR by 9 weeks, start of a new antineoplastic therapy due to efficacy concerns or death from any cause, whichever occurs first, based on IRC assessment	Table 7
Key secondary endpoints of relevance to the decision problem	Key secondary objectives: • Complete response rate (CRR) • Progression-free survival (PFS) • Overall Survival (OS) Other secondary objectives: • Duration of response (DOR) • Overall response rate (ORR) • PFS on next line of treatment (PFS-2) • Adverse events (AE) • Serious adverse events (SAE) • Health-related quality of life (HRQoL) Efficacy endpoints were based on IRC assessment	Table 7
Statistical analysis	Efficacy analyses used the ITT analysis set, and the safety analysis set was used to analyse safety. A hierarchical testing strategy was used for the primary and key secondary endpoints. The O'Brien-Fleming boundary alpha spending function was used to adjust for multiplicity. EFS (primary outcome) was analysed with a stratified Cox proportional hazards model. Kaplan-Meier product limit was used for time-to-event end points; time-to-event rates were computed using	B.2.4, Table 11, Table 12

	the Greenwood formula. HRs were estimated using a stratified Cox proportional hazards model. For OS, as patients from the SOC arm had the possibility to crossover to liso-cel, a 2-stage Weibull approach (2-stage accelerated failure time model), and a rank-preserving structural failure time model were investigated as supportive analyses. A Cochran-Mantel-Haenszel test with stratification factors as strata was used for CRR.	

1L: first line; ASCT: autologous stem cell transplant; CR: Complete response; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL3B: follicular lymphoma grade 3B; HDCT: High-dose chemotherapy; HGBCL: high grade B-cell lymphoma; ITT: Intention to treat; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; MYC: Myelocytomatosis oncogene; NHL: non-Hodgkin Lymphoma; NOS: not otherwise specified; PET: positron emission tomography; PD: Progressive Disease; PMBCL: primary mediastinal B-cell lymphoma; PR: Partial Response; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; sAAIPI: secondary age-adjusted International Prognostic Index; SD: Stable Disease; SOC: Standard of Care; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma.

[a] Block size of 4 with probability of 0.75 and block size of 6 with probability of 0.25.

[b] Refractory = stable disease, progressive disease, partial response or complete response with relapse before 3 months; relapse = complete response with relapse on or after lasting at least 3 months.

2.2.2 Eligibility criteria

The population in TRANSFORM is aligned with the population considered in the company's decision problem, which is narrower than the anticipated marketing authorisation and NICE scope (section 1.3). TRANSFORM included adults aged 18 to 75 years with LBCL who have relapsed within 12 months or are primary refractory to first line immunochemotherapy, and are eligible for ASCT. Eligibility for ASCT at the point of study entry was not defined in the trial protocol. In clarification A1, the company explained that TRANSFORM did not include any specific definition regarding eligibility for ASCT, but that the inclusion criteria specified that patients must be aged ≤75 years, have Eastern Cooperative Oncology Group (ECOG)

performance status ≤1 and have adequate organ function (see CS Table 7 for details). Eligibility for ASCT varies across the UK, but generally patients must be fit enough to receive platinum chemotherapy and have a sufficient enough response to proceed to ASCT. ASCT is usually only offered to patients under the age of 70 years, who must have adequate cardiac and renal function and be physically robust. In TRANSFORM, the definition of adequate organ function included creatinine clearance greater than 45 ml /min and left ventricular ejection fraction (LVEF) greater than >40% (see CS Table 7 for definitions of adequate organ function). In the UK, most centres would stipulate a creatine clearance greater than 50 to 60 ml/min and a LVEF greater than 45 to 50%, but this can vary. Specifically, the following types of LBCL were eligible:

- DLBCL not otherwise specified (NOS), de novo or transformed from indolent NHL
- HGBCL with rearrangements of MYC and either BCL2, BCL6, or both with DLBCL histology
- PMBCL
- T-cell histiocyte rich LBCL (THRBCL)
- FL3B

2.2.3 Interventions

Leukapheresis

All participants underwent leukapheresis prior to randomisation, and liso-cel manufacturing was performed for patients in both arms to enable rapid liso-cel infusion in cases of SOC failure. In Clarification A2, the company explained that in the case of a technical issue where the product could not be used (e.g. due to contamination or manufacturing failure), the patient could have a second collection procedure performed. A second leukapheresis procedure was required to manufacture liso-cel in [redacted] patients randomised to the liso-cel arm and treated with liso-cel, and in [redacted] patients randomised to the SOC arm who subsequently crossed over and were treated with liso-cel.

Liso-cel arm

Participants in the liso-cel arm received bridging therapy if needed, followed by lymphodepleting chemotherapy (LDC) and liso-cel:

- Bridging therapy was allowed for disease control during manufacture of liso-cel (after leukapheresis and prior to LDC) if deemed necessary by the investigator, using one cycle of one of the protocol-defined SOC regimen (see below). Local radiation was allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lesions were present. Bridging therapy is commonly used in NHS practice.[27]
- LDC consisted of cyclophosphamide and fludarabine administered for three days.
- Liso-cel was administered as two sequential IV infusions of CD8+ and CD4+ CAR T cells at a total target dose of 100 × 10^6 CAR T cells 2 to 7 days after completion of LDC. Liso-cel infusion was planned to occur 29 days +/-7 days after randomisation. The actual median time from randomisation to liso-cel infusion was [redacted] days (Clarification A2).

SOC arm

Participants in the SOC arm received re-induction therapy followed (if responded) by HDCT and ASCT:

- Re-induction therapy involved three cycles of one of three permitted SOC regimens (R-DHAP, R-ICE and R-GDP, see CS Table 7 for dose details). The EAG clinical experts considered the SOC regimens in TRANSFORM to be widely used in UK practice, with the choice of regimen depending on the preference of the centre. A switch within these SOC regimens was allowed in the event of toxicity or non-satisfactory response to the selected SOC regimen according to investigator judgement (this was not considered an EFS event). The CSR shows that [redacted]
- [redacted] ('other' was not defined). Although one EAG clinical expert considered these proportions and reasons for switching SOC to be reasonable, a second EAG expert noted that in the UK switching due to an suboptimal result would not occur as there is no

evidence to show superiority of one regimen over another, and that instead patients would be referred to third line CAR T. Switching would occur due to toxicity, but the proportion switching in TRANSFORM for this reason is slightly higher than expected. Participants who responded to re-induction therapy had one cycle of HDCT and ASCT.

Participants in the SOC arm could cross-over to liso-cel on request of the investigator if they met the criteria for LDC and liso-cel and if one of the following criteria was confirmed by the Independent Review Committee (IRC). There are no details in the CS or trial protocol regarding how often the IRC met to discuss each case. The criteria for eligibility of crossover were:

- Failure to achieve CR or PR by 9 weeks post-randomisation (after 3 cycles of SOC).
- Progression at any time.
- Need to start a new antineoplastic therapy due to efficacy concerns (absence of CR) after 18 weeks post-randomisation.

The company confirmed that there is no record of reasons why patients were not deemed eligible for crossover by the IRC (Clarification A8). Of the 61 patients in the SOC arm who were approved for crossover, the reasons were progression in [redacted], relapse in [redacted], and suboptimal response in [redacted] (Clarification A8). (Note that CS p108 states 60 patients in the SOC arm received liso-cel as a crossover treatment, however in Clarification A9 the company stated that 57/61 actually received liso-cel, with one further person receiving non-conforming product).

Non-conforming liso-cel product and second leukapheresis

In TRANSFORM, one participant in the liso-cel arm and one participant in the SOC arm who crossed over received a non-conforming liso-cel product. Non-conforming product occurs when the manufacture of liso-cel is attempted but is out of specification and so is not referred to as ‘liso-cel’. After careful expert consideration, non-conforming product may be used if it is thought to be in the best interests of the patient. The process for the decision to administer a non-conforming product was outlined in Clarification A3. The company stated that the time to infusion of the non-

conforming product was in line with that for those receiving a conforming product. For commercially-available liso-cel, the company described the process in the EU for managing non-conforming products, and stated that the process in the UK is still being established. The median turnaround time in days (from apheresis to qualifying product release) for out-of-specification liso-cel in Europe over the past 12 months is presented in Clarification 3 Table 1.

Additionally, five patients (3 liso-cel, 2 SOC) required a second leukapheresis for the successful manufacture of liso-cel. In practice, this delays patient access to treatment. The extent and impact of non-conforming product and repeat leukapheresis remains unclear of in real world use of liso-cel.

2.2.4 Risk of bias

The company assessed the risk of bias of TRANSFORM using the minimum criteria recommended by NICE (CS Table 13, CS Appendix 24). There are differences between the company's judgements in CS Table 13 and those in CS Appendix 24 for adequate random sequence generation, concealment of allocation, similarity of prognostic factors and imbalances in dropouts. In addition, it appears that the company confused concealment of treatment allocation with blinding of assigned interventions during the trial. The EAG therefore conducted an independent assessment of risk of bias using Cochrane RoB 2 criteria (Appendix 2). The EAG judged TRANSFORM to have a high risk of bias overall because of the risk of bias due to deviations from the intended interventions inherent in the design of TRANSFORM.

2.2.5 Baseline characteristics

A total of 184 people were randomised, with 92 participants in each arm. A CONSORT diagram is presented in CS Appendix Figure 2, with details of participant disposition tabulated in CS Appendix Table 71 and discussed under CS B.2.3.2. In the liso-cel arm, 89 participants received liso-cel and one participant received a nonconforming product. There was one study drug manufacturing failure and one participant withdrew consent before receiving liso-cel. In the SOC arm, 91 participants started SOC treatment. Of these, 61 (66.3%) patients were approved for switching to liso-cel treatment and 57 received liso-cel (plus one received a non-conforming product). See section 2.2.7 for further discussion on switching.

The CS presents demographic characteristics in CS Table 8 and disease characteristics in CS Table 9. Key characteristics from these are summarised in Table 5 below. The CS describes the demographic characteristics as 'reasonably well-balanced', however the EAG notes that the SOC arm had a higher proportion of patients aged under 65 years (liso-cel 60.9%, SOC 72.8%), with ECOG PS 0 at screening (liso-cel 52.2%, SOC 62.0%), (but not in ECOG PS at baseline, Table 5, suggesting some patients in the SOC arm worsened during the 28 day screening period), and who were men (liso-cel 47.8%, SOC 66.3%). The implications of this are not clear and the imbalances may be to chance. The CS reports that 'generally', UK clinical experts stated that the baseline demographic characteristics of patients in the TRANSFORM trial were aligned with those of patients in UK clinical practice. The EAG notes that both race and ethnicity were not reported by one quarter of participants.

The majority of participants had DLBCL NOS (liso-cel 57.6%, SOC 54.3%). Only 9.2% of all participants had PMBCL, five participants had THRBCL, and one participant had FL3B. Three quarters of participants were refractory to prior treatment, and one quarter of participants had relapsed disease.

In the liso-cel arm 58 (63.0%) participants received bridging therapy, in the SOC arm [redacted] of the participants who crossed over received bridging therapy (Clarification A13).

Table 5: **Key baseline characteristics**

Number of treated patients, n (%)	**Liso-cel (n=92)**	**SOC (n=92)**
Age, median (range: min, max)	60.0 (20, 74)	58.0 (26, 75)
Age category (years)		
<65 years	56 (60.9)	67 (72.8)
≥65 to <75 years	36 (39.1)	23 (25.0)
≥75 years	0	2 (2.2)
Male (at birth)	44 (47.8)	61 (66.3)
Race		
White	54 (58.7)	55 (59.8)
Asian	10 (10.9)	8 (8.7)

Black or African American	4 (4.3)	3 (3.3)
Not reported	22 (23.9)	25 (27.2)
Ethnicity		
Hispanic or Latino	3 (3.3)	3 (3.3)
Not Hispanic or Latino	65 (70.7)	62 (67.4)
Not reported	24 (26.1)	26 (28.3)
Unknown	0	1 (1.1)
ECOG performance status at screening		
0	48 (52.2)	57 (62.0)
1	44 (47.8)	35 (38.0)
ECOG performance status at baseline		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Hematopoietic cell transplantation-specific comorbidity index, median (Min, max)	[redacted]	[redacted]
Disease type at trial entry		
DLBCL	60 (65.2)	58 (63.0)
DLBCL NOS de novo	53 (57.6)	50 (54.3)
DLBCL from transformed indolent NHL	7 (7.6)	8 (8.7)
FL3B	1 (1.1)	0
HGBCL	22 (23.9)	21 (22.8)
PMBCL	8 (8.7)	9 (9.8)
THRBCL	1 (1.1)	4 (4.3)
Time from initial diagnosis to randomisation (months), median	7.57	7.72
sAAIPI at screening - n (%)		
0 or 1	56 (60.9)	55 (59.8)
2 or 3	36 (39.1)	37 (40.2)
Prior response status - n (%)		

Refractory	67 (72.8)	70 (76.1)
Relapse	25 (27.2)	22 (23.9)
Prior chemotherapy response status - n (%)		
Chemorefractory	26 (28.3)	18 (19.6)
Chemosensitive	66 (71.7)	74 (80.4)
Ann Arbor stage - n (%)		
Stage I	8 (8.7)	14 (15.2)
Stage II	16 (17.4)	15 (16.3)
Stage III	18 (19.6)	13 (14.1)
Stage IV	50 (54.3)	50 (54.3)

ECOG: Eastern Cooperative Oncology Group; liso-cel: lisocabtagene maraleucel; SOC: standard of care.
Source: CS Table 8, CS Table 9.

Prior chemotherapy regimens

In response to Clarification question A10, the company provided data on prior chemotherapy regimens. Participants received a wide range of chemotherapy regimens ([redacted] different regimens), with most regimens received by only one or two patients (data not tabulated here). The most frequently used regimens (used by at least 5% of either arm) are presented in Table 6. The most commonly used regimen was cyclophosphamide / doxorubicin / prednisone / rituximab / vincristine (liso-cel [redacted]), followed by cyclophosphamide / doxorubicin / etoposide / prednisone/ rituximab / vincristine (liso-cel [redacted], SOC [redacted]). No prior polatuzumab therapy was received by any participants in TRANSFORM.

Table 6: Prior anti-cancer therapies used by ≥5% of either arm, ITT set

Regimen, n (%)	**Liso-cel n = 92**	**SOC n = 92**
Systemic anti-cancer therapy	[redacted]	[redacted]
Cyclophosphamide/doxorubicin hydrochloride/prednisone/ rituximab/vincristine sulfate	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/etoposide/methotrexate/ prednisone/rituximab/vincristine	[redacted]	[redacted]

Cyclophosphamide/doxorubicin/etoposide/prednisone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisolone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisolone/ rituximab/vincristine sulfate	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisone/ rituximab/vincristine sulfate	[redacted]	[redacted]

2.2.6 Concomitant medications

CS Table 10 reports concomitant medications. These are generally balanced between groups, apart from antiparasitic products, insecticides and repellents, which were much higher in the liso-cel arm (liso-cel [redacted], SOC [redacted]). This classification includes drugs used to reduce the risk of pneumocystis pneumonia, a fungal infection of the lung, which is thought to persist for longer post CAR T than post ASCT.

Concomitant antineoplastic and immunomodulating agents

In response to Clarification question A14, the company provided data on use of concomitant antineoplastic and immunomodulating agents during TRANSFORM. Medications used in more than 5% of either arm are presented in

Table 7. Both arms show substantial use of concomitant antineoplastic and immunomodulating agents (liso-cel [redacted], SOC [redacted]), with filgrastim being the most commonly used (liso-cel [redacted] SOC [redacted]). There were imbalances between arms for some of the medications, including filgrastim-sndz (liso-cel [redacted], SOC [redacted]), pegfilgrastim (liso-cel [redacted], SOC [redacted]), and tocilizumab (liso-cel [redacted], SOC [redacted]).

Table 7: Concomitant medication: Antineoplastic and immunomodulating agents used by ≥5% in either arm, safety analysis set.

Drug class, n (%)	Liso-cel, n=92	SOC, n=91
Antineoplastic and immunomodulating agents	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]
Filgrastim-sndz	[redacted]	[redacted]
Granulocyte colony stimulating factor	[redacted]	[redacted]
Lenograstim	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Pegfilgrastim	[redacted]	[redacted]
Pegfilgrastim-cbqv	[redacted]	[redacted]
TBO filgrastim	[redacted]	[redacted]
Tocilizumab	[redacted]	[redacted]

2.2.7 Subsequent treatments

In response to Clarification question A11, the company provided data on use of subsequent anti-cancer therapies in TRANSFORM. At least one subsequent anticancer therapy was received by [redacted] of the liso-cel arm compared with [redacted] of the SOC arm (

Table 8). Systemic anti-cancer therapy was more common in the liso-cel arm than the SOC arm ([redacted] vs. [redacted]). As noted elsewhere (see section 2.2.5), a high proportion (65.2%) of the SOC arm crossed over to liso-cel, though [redacted]. Stem cell transplant was more frequent in the liso-cel arm than SOC ([redacted] vs. [redacted]), and radiation therapy was used only in the liso-cel arm ([redacted]). As the company notes in Clarification A11, participants received a wide range of subsequent chemotherapy regimens, with most regimens received by only one or two patients (data not tabulated here). The most commonly used regimen was bendamustine/polatuzumab vedotin/rituximab (liso-cel [redacted], SOC [redacted]).

Table 8: Subsequent anti-cancer therapies, ITT set

Drug type, n (%)	Liso-cel n = 92	SOC n = 92
Subjects with at least one subsequent anti-cancer therapy	[redacted]	[redacted]
Systemic anti-cancer therapy	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]
Autologous	[redacted]	[redacted]
Allogeneic	[redacted]	[redacted]
Radiation therapy	[redacted]	[redacted]
Cancer surgery	[redacted]	[redacted]
Cross over to Liso-cel	n/a	60 (65.2)
Other CAR T	[redacted]	[redacted]
Total Number of Subsequent Systemic Therapies Received (excluding CAR T, radiotherapy and SCT)	[redacted]	[redacted]

2.2.8 Clinical Results

The design of the TRANSFORM trial meant that people in the SOC arm were eligible to cross-over and receive liso-cel if they failed to achieve CR or PR after 3 cycles of SOC, if they progressed at any time, or needed to start a new antineoplastic therapy due to lack of CR at 18 weeks.

For some outcomes, this either led to people being censored from the respective analysis meaning the remaining sample is unbalanced, or people were not censored meaning the benefit from crossover being included in the analysis. Whilst the CAR T therapy is available on the NHS at 3rd line replicating the crossover, in the TRANSFORM trial people crossing over received it slightly quicker than in real-world use due to the manufacturing process occurring whilst they were receiving 2nd line SOC. Hence both approaches introduce bias into the analysis. The EAG requested some alternative analyses exploring the impact of varying the censoring rules.

The TRANSFORM trial recruited 184 people based on a hierarchical testing design. The null hypothesis for the primary endpoint EFS was tested first, and if rejected sequential testing was performed on CRR, PFS and OS.

The results of this submission come from the final efficacy analysis (data-cut October 2023), which contains over a year additional follow-up from the primary planned analysis (May 2022) and were published in Abramson 2023.[26]

Disease evaluations were performed at week 9 and week 18. At week 9, participants had received 3 cycles of SOC, or were 5 weeks post infusion of liso-cel. At week 18, participants were either 8 weeks post the start of HDCT or 14 weeks post liso-cel infusion.

A summary of results is provided in Table 9, however each outcome is discussed in more detail in the following sections.

Table 9: Summary of results from TRANSFORM[26]

	Primary Analysis	Final Data Cut [HR or RR (95% CI)])	EAG alternative analysis
Event Free Survival	0.36 (0.24, 0.52)	[redacted]	(no change)
CRR	1.70	[redacted]	N/A
ORR	1.78	[redacted]	N/A
PFS IRC	0.40 (0.26, 0.62)	[redacted]	[redacted]
PFS2	NR	[redacted][a]	N/A
OS	0.72 (0.44, 1.18)	[redacted]	N/A

a: the EAG is unclear exactly what analysis this point estimate relates to.

2.2.8.1 Primary Outcome - Event Free Survival

The primary outcome and other time-to-event outcomes were analysed using a stratified Cox model, stratified by the trial randomisation strata. In the company's analysis, EFS was defined as the time until progressive disease, or failure to achieve CR or PR at 9 weeks, or beginning a new antineoplastic therapy due to lack of CR, or death. People could be censored in this analysis if they failed to proceed to HDCT/ASCT, if no follow-up data was available, if they began a new antineoplastic therapy without lack of CR or at the last evaluation point is no event was observed. No p-value was provided for this outcome from the most recent data-cuts as significance was achieved during interim analysis 3, with a one-sided p-value < 0.0001 showing liso-cel superiority, as shown in Figure 1.[29] EFS is carried into the company's economic modelling to derive health states. The EAG notes that the company report in the cost-effectiveness section that the assumption of proportionality is violated for EFS. This means the hazard ratio may not give a reliable estimate of relative effect, however the EAG does not contest that a EFS benefit for liso-cel is clear.

Figure 1: Kaplan-Meier Plot for Event Free Survival from Transform Study (taken from Figure 6 of Company Submission)

EFS events were most commonly due to disease progression ( ) and failure to achieve at least PR by 9 weeks ( ).

The EAG requested alternative analysis where beginning a new therapy did not result in censoring/event (clarification A20), however this change had no effect on the results.

The EAG also requested information on the censoring rules (clarification A21). For EFS, of censoring events in the liso-cel arm were due to end of trial follow-up, and for the same reason in SOC arm. in both arms was censored at randomisation due to a lack of follow-up information.

2.2.8.2 Secondary Outcomes

2.2.8.2.1 Response Rates

People with unknown or missing response rates were classed as non-evaluable in this analysis. The company's description implies that responses to other antineoplastic therapies were included in this outcome if the subsequent therapy was started for reasons other than concerns over efficacy. It is unclear how many people had responses from subsequent therapies that were classed as responders. Aside from this potential issue, liso-cel achieved statistical significance for CRR at the time of the primary analysis (one-sided p<0.0001).

For liso-cel vs SOC, the CR rate was 68/92 vs 40/92 and the PR rate was [redacted]. These participants were included in the duration of response analysis which demonstrated a longer response for liso-cel ([redacted]), however this was not included in the formal hypothesis testing. The Kaplan-Meier plot for this analysis is shown in Figure 2, where loss of response can be seen to occur late in the follow-up for both arms. An analysis of the duration of only complete responses demonstrated a slightly larger difference ([redacted]).

[redacted]

Figure 2: Kaplan Meier plot of duration of response for all responders (taken from Figure 7 of Company Submission)

2.2.8.2.2 Progression-free survival

Whilst PFS is more commonly used than EFS, in this indication the company states the EFS is more relevant as treatments at this stage have curative intent, and so stable disease is not a successful outcome. The main difference between these outcomes is how people with stable disease were considered. Having stable disease beyond 9 weeks or beginning a new therapy due to loss of CR beyond 18 weeks did not count as an event in the PFS analysis.

For PFS, trial participants were censored if they received a new treatment, on the grounds that they would otherwise receive benefit from this subsequent treatment which would bias the comparison. The company states that the results remain biased as this censoring is informative as these censored patients are more likely to experience a later progression. The EAG accepts this could be an issue, however it is likely the magnitude of effect is small as the majority of EFS events were also disease progression events. People were also censored if they had no follow-up assessments, or did not experience a PFS event at the end of the trial follow-up.

Statistical significance was achieved for PFS in the primary data analysis, with one-sided p-value <0.0001.

As [redacted] censoring events on the SOC arm were due to beginning a new therapy, compared to [redacted] for liso-cel (clarification response Table 11), the EAG requested an alternative analysis where these people were not censored (clarification A20). As information on later disease progressions was available, the intention of the EAG was to capture a patients disease progression regardless of what therapies were received. However, the analysis performed by the company appears to directly replace these censoring events with a PFS event. As this appears to hold for every censored event visible on the Kaplan-Meier plot, the EAG is concerned over the validity of this analysis, and the possibility that PFS events have not been observed but instead has just been assumed to occur at the point of switching. The company's analysis is almost identical to the original EFS analysis, which is not what the EAG expected.

2.2.8.2.3 Progression-free survival on subsequent therapy (PFS2)

As described in the original CS, the desired PFS2 outcome is defined as “the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death from any cause.” The EAG interprets this to mean that a PFS2 event would be disease progression or death once a patient has switched treatments, regardless of whether they have already experienced a disease progression.

There was some confusion with this outcome as the TRANSFORM study originally defined as the “time from randomisation to second objective disease progression or death from any cause”, however this definition was less relevant for this appraisal. Some information provided by the company relates to this definition, rather than the one described in the CS.

The EAG focuses on the CS definition of PFS2, and notes it is perhaps the most important outcome, certainly for the cost-effectiveness modelling, as it includes the impact of subsequent therapies received, rather than this being a confounding effect. Given that participants receive potentially curative therapies at third line, it may be a better outcome from which to derive health states, rather than EFS. Despite this definition, the EAG remains uncertain over the analyses performed by the company relating to this outcome, as the information provided by the company suggests people in TRANSFORM could have multiple PFS2 events.

The company provided a Kaplan-Meier plot for this outcome (Clarification Response Figure 13) where a decreasing hazard rate can be seen, though no clear plateau is observed. The company did not provide an estimate of the hazard ratio and the plot did not contain censoring information, however the EAG was able to obtain a rough estimate of the unstratified hazard ratio by digitising the plot and fitting a Cox proportional hazards model which came out as [redacted]. Whilst this shows a benefit for liso-cel, the magnitude of the hazard ratio is different to the benefit estimated by the EFS outcome.

2.2.8.2.4 Overall survival

At the final data-cut, there were 34 death events in the liso-cel arm of TRANSFORM, and 42 death events in the SOC arm. The hazard ratio was not formally tested for significance at this stage, however the 95% confidence interval [redacted]. The company states that this is confounded by the crossover from SOC to liso-cel in the trial, potentially overestimating SOC OS and so underestimating the OS benefit of liso-cel. The EAG accepts this possibility however the impact may be small as CAR T therapy is permitted at 3rd line in NHS care. The difference in the trial was that CAR T was accessible more quickly meaning people may have been less ill when receiving it and slightly more people were well enough to receive CAR T. The EAG does not anticipate that the impact of this would sufficiently impact the hazard ratio to [redacted]. The Kaplan-Meier plot is shown in Figure 3, showing the potential for a small benefit for liso-cel, however the confidence intervals have not been included.

Figure 3: Kaplan Meier plot for overall survival from TRANSFORM (taken from Figure 9 of Company Submission)

The company performed analyses where the crossover effect was adjusted out by either the 2-stage or RPSFT approaches, however the EAG does not consider these relevant to this appraisal as subsequent CAR T therapy is routinely approved for NHS care.

2.2.8.3 Subgroups

The company conducted a series of subgroup analyses for the primary outcome (EFS). Across a range of patient characteristics, the stratified hazard ratio was generally consistent. For some minor subgroups (region=Japan, disease type=FL3B or THRBCL, age≥75), a benefit was not observed, however these may have occurred by chance and be explained by the very small sample size of the relevant subgroup. See Figure 19 of the company submission for more detail. The EAG requested results of bridging therapy subgroups, which were mentioned in the statistical analysis plan, but not included in the original submission. These were provided (clarification response A12), and the treatment effect appeared consistent.

2.2.8.4 HRQoL

The company used three questionnaires to capture quality of life information within the TRANSFORM study: EORTC QLQ-C30, FACT-Lym and EQ-5D-5L, see CS Section B.2.6.4.

Across each of these measures, the EAG notes that the completion rate for both arms for any evaluation point after baseline is below 50%. The baseline score completion rates are also low, and the EAG has major concerns over whether the whole patient experiences on either treatment arm are truly represented in the data. The EAG presents information on completion rates in

Table 10.

Table 10: Number of responses for HRQoL outcomes in TRANSFORM at select evaluation points.

		Baseline Score	9 Weeks	18 Weeks	12 Months	24 Months	36 Months
EORTC QLQ C30 Global	Liso-cel (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SOC (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACT Lym	Liso-cel (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SOC (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L	Liso-cel/SOC combined (n=184)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: the EAG obtained these values from the CSR Table 14.3.5.11.1.1 but notes that for later time points the CSR provided differing values for the number of responses.

The EAG understands that data were not collected after crossover and so people who crossed-over to liso-cel are effectively excluded from the analysis beyond this point.

Across the EORTC QLQ-C30 domains presented by the company (global, fatigue, pain, physical functioning, cognitive function; Company Submission Figures 10-14), there was no clear long-term difference between arms from those contributing information to the analyses.

For FACT-Lym lymphoma subscale, the limited data from TRANSFORM suggested a deterioration beyond the minimally important difference for SOC which did not occur for liso-cel.

For EQ-5D-5L, the company first presented pooled data from both arms of the trial, which showed a weak increasing trend in quality of life over time, however this may be attributable to attrition bias. A comparison of the two arms showed that SOC consistently had a higher quality of life, however this might be attributable to the likely imbalance of patient characteristics, rather than the intervention.

The EAG concludes that there is no evidence to suggest people who achieve a good response to either liso-cel or SOC have a different quality of life based on the

treatment they receive. There is no evidence from the trial on quality of life for later lines of therapy.

2.2.8.5 Overview of adverse events in TRANSFORM

Treatment emergent adverse events (TEAEs) were presented for the safety analysis set (SAS), which included all participants who had taken at least one dose of study treatment. Reporting was done against the actual treatment received. For the SOC arm (n=91), the SAS was patients who received any treatment (e.g. re-induction immunochemotherapy with or without HDCT or ASCT). For the liso-cel arm (n=92), this was patients who received any study treatment, including bridging therapy if needed, lymphodepleting CT, and liso-cel or non-conforming product.

The EAG notes that the FDA clinical review considered there was limited use in comparing toxicities between the two treatment arms in TRANSFORM. They noted two considerations: '*1) Significant heterogeneity in the standard therapy arm in terms of exposure, the toxicities reported for this arm do not reflect the intended treatment plan and are likely underrepresented 2) The two arms have fundamentally different treatment modalities that have distinct toxicity profile'.*[30] The EAG agrees with this view.

The following sections summarise TEAEs occurring in TRANSFORM. See section 2.5.3 for a summary of TEAEs occurring in other liso-cel studies.

2.2.8.6 Summary of TEAEs

An overview of TEAEs is presented in Table 11. At least one TEAE was experienced by 98.9% of the SOC arm and 100% of the liso-cel arm, and Grade 3/4 events were experienced by 89.0% and 92.4%, respectively.

Deaths occurring in the SOC arm are presented separately for those occurring prior to receiving crossover therapy (9.9%) and those occurring after cross-over (56.9%) (Table 12). There were 34 (37.0) deaths in the liso-cel arm. Causes of death by category is also presented in Table 12.

Table 11: Overall summary of TEAEs in TRANSFORM, SAS

Category	SOC (n=91) n (%)	Liso-cel (n=92) n (%)
All TEAEs	90 (98.9)	92 (100)
All Grade 3/4 TEAEs	81 (89.0)	85 (92.4)
All TEAEs (related to any drug)	[redacted]	[redacted]
All TESAEs	[redacted]	[redacted]
All TESAEs (related to any drug)	[redacted]	[redacted]
All TEAEs leading to withdrawal of any study drug	[redacted]	[redacted]
All TEAEs leading to dose interruption of any study drug	[redacted]	[redacted]

AE: adverse event; SAS: safety analysis set; SAE: serious adverse event; SOC: standard of care; TEAE: treatment emergent adverse event; TESAE: treatment emergent serious adverse event.
Source: Reproduced from CS Tables 26.

Table 12: **Overall summary of deaths, SAS**

	SOC Prior to crossover (n=91) n (%)	SOC Post-crossover (n=58) n (%)	Liso-cel (n=92) n (%)
Deaths	9 (9.9)	33 (56.9)	34 (37.0)
Causes of death by category			
Death from malignant disease under study, or complication due to malignant disease under study	[redacted]	[redacted]	[redacted]
Death from AE (not otherwise specified)	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to death	[redacted]	[redacted]	[redacted]

AE: adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 27.

2.2.8.7 Common TEAEs and Grade 3/4 AEs

The most frequent TEAEs of any grade and of Grade 3/4 are presented in Table 13. In the SOC arm, the most frequent events of any grade were thrombocytopenia (72.5%), anaemia (68.1%), nausea (58.2%), neutropenia (54.9%) and diarrhoea ([redacted]%). The most common Grade 3/4 events were thrombocytopenia (68.1%), anaemia (56.0%); neutropenia (51.6%) and febrile neutropenia ([redacted]%). In the liso-cel arm, the most frequent events of any grade were neutropenia (82.6%), anaemia (67.4%), thrombocytopenia (59.8%), nausea (53.3%) and CRS (48.9%); and the most frequent Grade 3/4 events were neutropenia (81.5%), anaemia (52.2%) and thrombocytopenia (50.0%).

Table 13: **Incidence of TEAEs occurring in ≥ 20% of patients in either treatment group, SAS**

TEAE	SOC (n=91) n (%)		Liso-cel (n=92) n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	66 (72.5)	62 (68.1)	55 (59.8)	46 (50.0)
Anaemia	62 (68.1)	51 (56.0)	62 (67.4)	48 (52.2)
Nausea	53 (58.2)	4 (4.4)	49 (53.3)	3 (3.3)
Neutropenia	50 (54.9)	47 (51.6)	76 (82.6)	75 (81.5)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	38 (41.8)	2 (2.2)	37 (40.2)	0 (0.0)
Decreased appetite	32 (35.2)	4 (4.4)	21 (22.8)	1 (1.1)
Vomiting	27 (29.7)	2 (2.2)	18 (19.6)	1 (1.1)
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	24 (26.4)	0 (0.0)	30 (32.6)	2 (2.2)
Pyrexia	23 (25.3)	0 (0.0)	28 (30.4)	0 (0.0)
Hypokalaemia	22 (24.2)	4 (4.4)	21 (22.8)	4 (4.3)
Hypomagnesaemia[a]	21 (23.1)	1 (1.1)	15 (16.3)	0
Headache	21 (23.1)	1 (1.1)	40 (43.5)	4 (4.3)
Dizziness	13 (14.3)	0 (0.0)	22 (23.9)	0 (0.0)
Lymphopenia	11 (12.1)	9 (9.9)	25 (27.2)	24 (26.1)

Insomnia	10 (11.0)	0 (0.0)	19 (20.7)	0 (0.0)
Hypotension	6 (6.6)	0 (0.0)	19 (20.7)	3 (3.3)
Cytokine release syndrome	0 (0.0)	0 (0.0)	45 (48.9)	1 (1.1)

TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 28. [a] From CSR.

2.2.8.8 Adverse events of special interest

Adverse events of special interest (AESI) are summarised in Table 14. The most common AESI events of any grade in the liso-cel arm were neurological toxicity ([redacted]), CRS (48.9%), and prolonged cytopenia (43.5%). The most common Grade ≥3 events in the liso-cel arm were prolonged cytopenia ([redacted]), severe infections ([redacted]), and neurological toxicity ([redacted]).

Further details of AESIs following liso-cel are presented in CS Table 30 for neurological toxicity immune effector cell-associated events (any: 10.9%; Grade 3/4: (4.3%); clear definitions for this and for neurological toxicity as reported in the above paragraph are not provided in the CS. CS Table 31 reports details of CRS, and details of any grade infections and infestations in both arms are provided in CS Table 32.

Table 14: **Incidence of AESIs in either treatment group, SAS**

AESI	**SOC (n = 91) n (%)**	**Liso-cel (n = 92) n (%)**
All AESIs	[redacted]	[redacted]
All Grade 3/4 AESIs	[redacted]	[redacted]
All AESIs related to any study drug	[redacted]	[redacted]
All serious AESIs	[redacted]	[redacted]
All serious AESIs related to any study drug	[redacted]	[redacted]
All AESIs leading to death	[redacted]	[redacted]
All AESIs leading to withdrawal of any study drug	[redacted]	[redacted]

All AESIs leading to dose interruption of any study drug	[redacted]		[redacted]	
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**
Neurological toxicity	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Cytokine release syndrome	0 (0.0)	0 (0.0)	45 (48.9)	1 (1.1)
Prolonged cytopenia	3 (3.3)	3 (3.3)[a]	40 (43.5)	40 (43.5)[a]
Severe infections	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]
Infusion Related Reaction (IRR)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Second Primary Malignancy	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Tumour Lysis Syndrome (TLS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Macrophage Activation Syndrome (MAS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]

[a]Based on March 2022 DCO, as breakdown of Grade 3/4 AESIs were not reported in the final DCO (October 2023). There were no changes in any grade AESIs between March 2022 and October 2023 data cuts.
Abbreviations: TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 29: the company confirmed in Clarification response A16 that the data in CS Table 29 are correct, and that text in section B.2.10.3 stating 'AESIs of Grade 3/4 occurred in [redacted] patients ([redacted]%) who received liso-cel and [redacted] patients (55.4%) who received SOC' incorrectly attributed these values to the opposite trial arms.

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

No indirect comparison was performed in this appraisal.

2.4 *Critique of the indirect comparison and/or multiple treatment comparison*

No indirect comparison was performed in this appraisal.

2.5 *Additional work on clinical effectiveness undertaken by the EAG*

2.5.1 EAG updated searches

The EAG information specialist conducted an SLR update to identify additional publications since the last CS SLR searches undertaken in February 2024. The search strategies are reported in 7.3 Appendix 3. The EAG update search focused on SCT-eligible R/R LBCL patients receiving 2L treatment. All records identified through electronic database searches were assessed against the CS eligibility criteria by two independent EAG reviewers. The EAG screened 456 articles against the clinical effectiveness eligibility criteria. Of these, 24 were identified for potential retrieval of full texts; however, after a consensus discussion, none were ultimately retrieved as only two articles were related to liso-cel and neither provided any new information of relevance to the appraisal.

2.5.2 Additional liso-cel studies

As stated in Section 2.1.1, of the original 124 studies included in the company SLR only one was considered as relevant to inform the clinical evidence for the appraisal.[26] The EAG checked the details of the remaining 123 studies and requested summary details of two observational studies of CAR T therapies in clarification A6. The two observational studies,[31, 32] provide insights into real-world clinical effectiveness and safety of 2L CAR T therapy for LBCL, but the data presented for liso-cel in these two conference abstracts were limited.

The observational study by Dahiya (2023)[31] was conducted across five US academic institutions and retrospectively analysed data from 112 LBCL leukapheresed patients who received commercial CAR T therapy (9 liso-cel) between April 2022 and April 2023. The key findings for ORR, remission, PFS and OS were not provided for the liso-cel participants, and the efficacy results are of limited value to the current appraisal (see Clarification response A6 for further details). No deaths related to CRS or ICANS were reported.

The observational study by Koff (2023)[32], used data from eight US academic centres for Lymphoma Epidemiology of Outcomes (LEO) Cohort study and the Consortium for Real World Evidence (CReWE). The cohort included 1523 patients with

relapsed/refractory LBCL, aged ≥ 18 years, receiving 2L systemic therapy from 2002 to 2022. Only 88 participants received CAR T therapies at second-line, many during clinical trials, and no data were presented by the type of CAR T therapy received. As such the results are of limited value to the current appraisal (summarised in Clarification response A6).

The EAG agrees with the company that there are no relevant liso-cel data to include from these conference abstracts.

2.5.3 Adverse events in the literature

The EAG searched for additional data on AEs associated with liso-cel, and presents a summary of findings here.

A recent systematic review (Yamshon 2024[33]) compared the incidence of CRS, immune effector cell associated neurotoxicity syndrome (ICANS), hematologic toxicity, and infections associated with FDA- approved CAR T products for NHL.

Four liso-cel studies were included (the EAG notes that Cohort 1 – Europe (n=27) of the TRANSCEND WORLD study[34] was not included):

- TRANSFORM interim analysis (Kamdar 2022[29]), n=90
- TRANSCEND (Abramson 2022[35]), n=269
- PILOT (Sehgal 2022[36]), n=61
- TRANSCEND WORLD Cohort 3 - Japan (Makita 2022[37]), n=10

The review also included six axicabtagene ciloleucel studies and five tisagenlecleucel studies, but these are not summarised here. Results for liso-cel and are summarised in Table 15.

There was little statistical heterogeneity between the liso-cel studies for any grade and Grade ≥3 CRS, indicating the incidence of events was similar between studies. There was moderate statistical heterogeneity for Grade ≥3 ICANS and Grade ≥3 Infection, and considerable statistical heterogeneity for the other events (Table 15), suggesting differences in incidence between studies. However, there was no clear pattern (e.g. whether events were lower or higher in TRANSFORM) and the clinical impact of this is unclear. In addition, the FDA clinical review considered the key

adverse events to be comparable across the three studies they considered[30] (see below).

Yamshon 2024[33] note a number of limitations to their analysis, such as differences across the trials in inclusion criteria, adverse event grading scales, and toxicity treatment practices. Results should therefore be viewed with caution.

Table 15: **Summary of results of pooled incidence rates of AESIs for liso-cel**

	Pooled incidence rate, % (95% CI) Heterogeneity, I^2
	Liso-cel 4 studies, n=430
CRS – any grade	43 (38, 49) I^2 = 8%
CRS - grade ≥3	1 (0.1, 0.3) I^2 = 0%
ICANS – any grade	22 (12, 34) I^2 = 79%
ICANS – grade ≥3	6 (3, 10) I^2 = 30%
Anaemia – any grade	3 studies, n not reported 49 (17, 63) I^2 = Not reported
Anaemia – grade ≥3	39 (17, 63) I^2 = 91%
Thrombocytopenia – any grade	3 studies, n=340 47 (12, 84) I^2 = 87%
Thrombocytopenia – grade ≥3	38 (19, 59) I^2 = 88%
Neutropenia – any grade	3 studies, n=340 64 (46, 81) I^2 = 70%
Neutropenia – grade ≥3	69 (50, 86) I^2 = 89%
Infection – any grade	1 study, n=10 10 (3, 45)
Infection – grade ≥3	11 (8, 14) I^2 =34%
Febrile neutropenia – any grade	3 studies, n=420 8 (2, 17) I^2 = 79%

Data from Yamshon 2024[33]

FDA clinical review

The FDA clinical review[30] pooled safety data from three liso-cel studies (n=418):

- TRANSFORM interim analysis (Kamdar 2022[29]), n=89
- TRANSCEND (Abramson 2022[35]), n=268
- PILOT (Sehgal 2022[36]), n=61

Non-fatal serious adverse events are summarised in Table 16, Grade ≥3 AEs occurring among the 418 pooled participants are presented in Table 17, and AESI are presented in Table 18. The FDA reviewer noted that key AEs were comparable across the three studies. The EAG noted some slight differences in the proportion of pooled adverse events between the FDA clinical review and the Yamshon 2024[33] systematic review, e.g. for CRS. It is unclear whether this is due to an error, recoding of adverse events in the FDA review, or some other reason.

Table 16: Non-fatal serious adverse events in liso-cel studies

System Organ Class and Preferred Term, n (%)	TRANSFORM N=89	PILOT N=61	TRANSCEND N=268	Total N= 418
Subjects with any serious TEAE	34 (38)	20 (33)	122 (46)	176 (42)
Blood and lymphatic system disorders	14 (16)	1 (2)	25 (9)	35 (8)
Febrile neutropenia	14 (16)	1 (2)	25 (9)	40 (10)
Immune system disorders	12 (14)	8 (13)	49 (18)	69 (17)
Cytokine release syndrome	12 (14)	8 (13)	49 (18)	69 (17)
Nervous system disorders	5 (6)	1 (2)	41 (15)	47 (11)
Encephalopathy	2 (2)	1 (2)	12 (5)	15 (4)
Aphasia	2 (2)	0	9 (3)	11 (3)
Tremor	1 (1)	0	3 (1)	4 (1)
Infections and infestations	14 (16)	5 (8)	28 (10)	47 (11)
Infections with pathogen unspecified	7 (8)	3 (5)	24 (9)	34 (8)
Bacterial infectious disorders	5 (6)	2 (3)	14 (5)	22 (5)
Viral infectious disorders	3 (3)	0	4 (2)	7 (2)
Fungal infectious disorders	0	0	3 (1)	3 (1)
Psychiatric disorders	0	3 (5)	20 (8)	23 (6)
Confusional state	0	3 (5)	8 (3)	11 (3)
Mental status changes	0	0	7 (3)_	7 (2)

Respiratory, thoracic and mediastinal disorders	2 (2)	2 (3)	12 (5)	16 (4)
Pulmonary embolism	2 (2)	2 (3)	1 (0.4)	5 (1)
Dyspnea	0	0	15 (6)	15 (4)

Source: FDA Clinical Review[30]

Table 17: **Grade ≥3 AEs in ≥2% of 418 participants (3 studies) with liso-cel**

Grade ≥3 AEs, n (%)	**Pooled studies n=418**
Infections - pathogen unspecified	65 (16)
Encephalopathy	45 (11)
Sepsis	27 (6)
Dyspnea	24 (6)
Hypertension	22 (5)
Pneumonia	21 (5)
Musculoskeletal pain	19 (5)
Hypotension	19 (5)
Bacterial infection	19 (5)
Fatigue	18 (4)
Cytokine release syndrome	16 (4)
Abdominal pain	16 (4)
Edema	15 (4)
Dizziness	15 (4)
Aphasia	14 (3)
Decreased appetite	13 (3)
Delirium	12 (3)
Urinary tract infection	11 (3)
Headache	10 (2)
Renal failure	10 (2)
Motor dysfunction	10 (2)
Cardiac Arrhythmias	9 (2)
Gastrointestinal haemorrhage	9 (2)
Nausea	8 (2)
Thrombosis	8 (2)
Hemophagocytic lymphohistiocytosis	7 (2)

Source: FDA Clinical Review[30]

Table 18: **AESI among 418 participants (3 studies) with liso-cel. pooled studies, n=418**

TEAEs	**Grade 1-5**	**Grade ≥3**
Subjects with any CRS	191 (46)	15 (3.5%)
CRS symptoms		

fever	183/191 (96)	11/191 (6)
hypotension	83/191 (43)	11/191 (6)
tachycardia	55/191 (29)	1/191 (1)
chills	44/191 (23)	0
hypoxia	32 (17)	14 (7)
Headache	24 (13)	5 (3)
Fatigue	24 (13)	1 (1)
Subjects with any neurologic toxicity (NT)	136 (33)	42 (10)
NT symptoms		
Encephalopathy	83 (20)	25 (6)
Tremor	45 (11)	1 (0)
Aphasia	30 (7)	9 (2)
Headache	24 (6)	5 (1)
Dizziness	22 (5)	2 (0)
Delirium	21 (5)	5 (1)
Ataxia	17 (4)	1 (0)
Neuropathy peripheral	4 (1)	0 (0)
Motor dysfunction	3 (1)	1 (0)
Paresis	3 (1)	2 (0)
Seizure	3 (1)	3 (1)
Infections	170 (41)	54 (13)
Bacterial infections	56 (13)	22 (5)
Infections – pathogen unspecified	82 (20)	34 (8)
Febrile neutropenia	40 (10)	40 (10)
Fungal infections	45 (11)	2 (0.5)
Viral infections	11 (3)	8 (2)
Prolonged cytopenias[a]	382 (91)	157 (38)
Neutropenia	373 (89)	94 (22)
Thrombocytopenia	172 (41)	127 (30)
Anemia	139 (33)	31 (7)
Hypogammaglobulinemia	62 (15)	1 (0)
Myelodysplastic syndrome	8 (2)	8 (2)

[a]not resolved by day 29 post lisocabtagene maraleucel infusion

TRANSCEND FL study

TRANSCEND FL[38] was a Phase 2 study (n=130) of liso-cel for R/R FL, including third line patients and second line with progression of disease within 24 months from first-line immunochemotherapy. Rates of any grade CRS were slightly higher in

TRANSCEND FL than in TRANSFORM, but rates of neutropenia, anaemia, thrombocytopaenia and prolonged cytopenia were lower in TRANSCEND FL.

Table 19: **Key AESI reported in TRANSCEND FL**

	2L+ FL, n=130	
TEAE, n (%)	**Any grade**	**Grade ≥3**
Neutropenia	85 (65)	76 (58)
Cytokine release syndrome	75 (58)	1 (1)
Neurological event [a]	20 (15)	3 (2)
Anaemia	49 (38)	13 (10)
Thrombocytopenia	33 (25)	13 (10)
Prolonged cytopenia [b]	-	29 (22)
Severe infections	-	7 (5)
Hypogammaglobulinemia	6 (5)	-
Second Primary Malignancy	4 (3)	-
Macrophage Activation Syndrome / hemophagocytic lymphohistiocytosis	1 (1)	-

[a] investigator identified neurological AEs related to liso-cel. [f] Defined as grade ≥3 laboratory abnormalities of neutropenia, anaemia or thrombocytopenia on day 29.

2.6 *Conclusions of the clinical effectiveness section*

The CS presents direct evidence from the TRANSFORM trial, an open-label Phase III multinational RCT comparing liso-cel with SOC in people with R/R LBCL who are eligible for ASCT.

A statistically significant improvement was found with liso-cel compared with SOC in the primary outcome EFS (HR [redacted]), and secondary outcomes CRR (RR [redacted]), ORR (RR [redacted]), PFS (HR [redacted]) and PFS2 (HR [redacted]). The HR for OS [redacted] (HR [redacted]). The most frequent Grade 3/4 events in the liso-cel arm were neutropenia (81.5%), anaemia (52.2%) and thrombocytopenia (50.0%); in the SOC arm they were thrombocytopenia (68.1%), anaemia (56.0%) and neutropenia (51.6%).

The population in the TRANSFORM trial and the company's decision problem is narrower than that defined by the NICE scope. The EAG considers TRANSORM to have a high risk of bias due to deviations from the intended interventions allowed by the trial design. A high proportion (66.3%) of participants in the SOC arm were

eligible to crossover to liso-cel as part of the trial design. Approaches to censoring of these data may have introduced bias into the analysis.

Alternative analyses requested by the EAG had no effect on the EFS results, however the EAG has concerns with the validity of additional analyses requested for PFS. The EAG considers that PFS2 may be a more appropriate outcome than EFS for deriving health states, and notes that the magnitude of the HR is different to the benefit estimated by the EFS outcome. HRQoL data were presented in the CS but the EAG notes that completion rates were low and that data were not collected after crossover. Overall, the EAG considers that there is no evidence to suggest a difference between treatments in the quality of life of people who achieve a good response.

Generalisability issues:

There are a number of generalisability issues that the EAG believe important to consider when applying the results of TRANSFORM to UK clinical practice. In general, the EAG clinical experts are of the opinion that the baseline characteristics of TRANSFORM are broadly representative of people with R/R LBCL seen in clinical practice in the UK. The EAG considers that the proportion of participants receiving bridging therapy is lower than in UK practice, discussed further in Section 3.2.8.1.2. The options for first line treatment in the UK has changed since TRANSFORM commenced with a greater number of people anticipated to receive Pola+R-CHP at first line since the 2023 NICE recommendation, whilst [redacted] participants received prior Pola+R-CHP in TRANSFORM. The EAG also notes that in the SOC arm of TRANSFORM the time from confirmation of eligibility for crossover to administration of liso-cel was much quicker than would occur in clinical practice. Additionally, there was very little drop-out between leukapheresis and infusion in the liso-cel arm, with advice to the EAG suggesting this is not reflective of practice in real world settings. Finally, the subsequent therapies received in TRANSFORM are not reflective of recently approved therapies or UK practice (discussed further in Section 3.2.8.3), including the likelihood of liso-cel arm receiving a second CAR T treatment, and proportions receiving CAR T following SOC.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

3.1.1 Search strategy

Searches for cost-effectiveness and health-related quality of life (HrQoL) evidence were carried out separately in April 2020 on an appropriate selection of bibliographic databases, conference websites and grey literature sources, including websites of relevant HTA organisations. The searches were updated and re-run 5 times, the latest search was in February 2024 (CS Appendix G.1.1 Search strategy Tables 26-36 and H.1.1.1 Tables 48-56). The searches were limited to 2003 onwards as the first trial for rituximab (standard of care in newly-diagnosed LBCL) was published in 2002. The EAG note that it was reasonable to limit the searches for this reason. A supplementary search was carried out with the inclusion of additional economic terms with no date limit (CS Appendix G 1.1. Table 37).

The database search strategies are appropriately comprehensive and well-constructed. The searches include database-specific indexing and free-text terms for the population/ condition (R/R DLBCL) combined with filters for costing, economic and HRQoL studies (CS Appendix G.1.1.1 Search strategy Tables 26-36 and Tables 48-56). Omitting terms related to the intervention/ treatment type increases the sensitivity of the searches. The reasonably sensitive and non-validated search filters developed by CADTH (Canadian Agency for Drugs and Technologies in Health),[39] the validated NHS EED Economic filter[40] and the validated balanced McMaster filter[41] for economic and costing studies were applied (CS Appendix G.1.1.1 Electronic database searches Tables 27-36). The sensitivity maximising validated search filter developed by Arber et al (2017)[42] for health state utility values (HSUVs) was applied to the search for health-related quality of life studies (CS Appendix H.1.1.1 Electronic database searches Tables 48-56).

The search terms used for the retrieval of grey literature and conference sources are provided but the numbers of retrieved and included results are not (CS Appendix G.1.1.2 Grey literature, conference and other website searches Tables 37 and 38

and H.1.1.2 Grey literature, conference and other website searches Tables 57 and 58). The full details of the reviews examined in the hand-searches are also not reported (CS Appendix G.1.2 Study selection). Only conference proceedings from 2016 onwards were searched and conference abstracts published prior to 2018 were sought via hand-searches (CS Appendix G.1.2.1 Eligibility criteria Table 39). A search of older conference proceedings may have identified additional trials that were never published, to counter publication bias (H.1.1.2 Grey literature, conference and other website searches Tables 57 and 58).
The EAG had no further concerns with the company's search.

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

3.2.1 NICE reference case checklist

Table 20: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. A 50-year time horizon was used. The EAG considers this long enough to reflect all differences in costs and outcomes.
Synthesis of evidence on health effects	Based on systematic review	Utility values were derived from the TRANSFORM trial and ZUMA-1 3L axi-cel trial, TA895 for relevant scenario analyses.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. EQ-5D data were used to derive health effects

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rates should be applied per cycle rather than annually. Weekly discount rates should be applied for the first 5 years of the model cycle. Afterwards, annual discount rates should be applied in line with the model structure.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company used a partitioned survival model with three health states:

- Event-free (2L): patients who are alive and event-free
- Post-event (3L+): patients who are alive and have experienced an event
- Death: patients who have died

The cost-effectiveness of liso-cel is based on the TRANSFORM trial. EFS is the primary end point of the trial, defined as the time from randomisation to progressive disease, failure to achieve CR or PR by 9 weeks or the start of new antineoplastic therapy due to efficacy concerns or death, whichever occurs first.

The EFS curve determined the proportion remaining alive and event free. The OS curve determines the proportion of patients alive regardless of event status and the post-event state was calculated as the difference between the OS and EFS state.

The EFS data is mature but median OS was not reached. Mixture cure models were fitted to the EFS and OS TRANSFORM trial using the final DCO (October 2023). Mixture cure models divide the population into two groups: those who are 'cured' and those who are not. The probability of 'cure' is estimated by parametric models. The proportion of patients who experience 'cure' are subject to SMR of 1.09 and age and gender matched general population mortality risk. Mortality risk for those who do not experience cure is defined as parametric curves fitted to the TRANSFORM data.

Parametric models fitted to the EFS curve predicted a cure rate ranging from [redacted]% to [redacted]% for liso-cel and [redacted] to [redacted]% for SOC. The company prefers the log-normal model for both liso-cel and SOC EFS extrapolation with a predicted EFS cure fraction of [redacted]% in the liso-cel arm and [redacted]% in the SOC arm.

Parametric curves fitted to the OS data predicted OS cure fraction ranging from 55.8% to 63.4% for liso-cel and 50.7% to 54.5% for SOC. Similar to the EFS, curve, the company prefers the log-normal model for extrapolation OS in both arms which predicted an OS cure fraction of 60.3% and 51% respectively. Parametric models were chosen based on considerations of visual fit, statistical fit using AIC and BIC criteria, plausibility of long-term extrapolations for combined cured and non-cured fractions, predicted cure fractions and plausibility of extrapolation for non-cured patients and plausibility of hazard functions.

TTNT data were used to determine the timepoint for initiating next treatment which were applied as a single one-off cost in the post-event health state. TTNT was defined as the time from randomisation to death or the start of new antineoplastic therapy whichever occurred first. Parametric curves were fitted to the TTNT KM data for each arm. Parametric models were chosen based on visual inspection of fit, plausibility of long-term extrapolations for combined cured and non-cured population, plausibility of extrapolation for non-cured population and statistical fit using AIC and BIC criteria.

Intervention costs include CAR T tariff costs, bridging therapy and drug acquisition costs. CAR T tariff costs were assumed to include pre-treatment (leukapheresis and

lymphodepleting chemotherapy), treatment (liso-cel drug administration costs) and post liso-cel infusion cost (resource use and AE management costs up to 100 days after infusion). Patients who discontinued treatment prior to liso-cel infusion were assumed to incur bridging therapy and leukapheresis costs. SOC cost include drug acquisition and administration costs associated with re-induction immune chemotherapy as well as HDCT and ASCT. After progression from the event-free state, patients in the liso-cel arm assumed to receive SCT, chemotherapy and radiotherapy at 3L+. Patients in the SOC arm are assumed to receive SCT, chemotherapy and CAR T at 3L. A detailed breakdown of the proportion of patients receiving each treatment is presented in subsequent sections. Resource use was estimated from NHS reference cost and estimates used in previous appraisals. All costs were inflated appropriately to reflect current prices.

Quality of life values were derived from the TRANSFORM trial using the EQ-5D-5L data cross-walked to the 3L using standard algorithm. Regression models were fitted with baseline utility and other co-variates as predictors. A summary of the model base-case assumptions and inputs is presented in CS Table 70.

In the opinion of the EAG, progression from EFS state to a post-event health state does not reflect an objective change in health status. For example, a patient with stable disease in the event free health state transitions to a post-event health state after 9 weeks without an underlying worsening of prognosis. Furthermore, it does not appropriately consider for the possibility of cure at 3L+ which may bias the ICER. Patients in the trial receive curative therapy, including CAR T for SOC at 3L+. The difference between the EFS and OS cure fraction in the SOC group ([redacted] vs 51%), suggests that a significant proportion of patients in the SOC group will be cured at 3L+. Hence, patients in the SOC group who experience cure at 3L+ do not receive the corresponding health benefits associated with cure as they remain in the post-event state.

For these reasons, the EAG requested an alternative end point be implemented in the economic model. The model was partitioned into a pre-PFS-2 health state (encompassing 2L and 3L treatment) and a post PFS-2 health state (i.e. fourth-line patients). This allows patients to receive treatment with curative intent in both 2L and 3L settings. Resource use was estimated based on the EFS health state occupancy, but health outcomes were based on the PFS-2 heath state. A detailed critique of the

treatment effectiveness and extrapolation is presented in Section 3.2.6. Whilst an EFS-based model was accepted in TA895, it is not clear whether any suitable alternatives were available for consideration.

3.2.3 Population

The population modelled was based on the TRANSFORM trial. Patient baseline characteristics used in the model were derived from the TRANSFORM trial as presented in Table 7 above. The EAG considers the population largely appropriate for decision making. The EAG considers the starting age of the population ([redacted]) to be younger than the expected age of a UK relevant population. The starting age of a similar appraisal, TA895, had a starting age of 57.2 based on the mean age of the population in ZUMA-7. Data provided by NHS England suggests that the mean age of people who have received 2L axi-cel since it entered the CDF is 59 years old (based on data analysed on 17th July 2024), and the EAG uses this value in its base case analysis.

3.2.4 Interventions and comparators

Patients in the intervention group were split into those who received liso-cel infusion (97.8%) and those who did not receive liso-cel infusion (2.2%). Infused patients were modelled to incur the full cost of liso-cel and non-infused patients were modelled to incur the cost of leukapheresis and bridging chemotherapy. Of the 90 infused patients, one patient received a non-conforming product infusion. Costs associated with CAR T acquisition for patients who received a non-conforming product were not accounted for, although administration costs were included in line with patients receiving liso-cel.

Patients in the comparator group were modelled to receive SOC which included re-induction immunochemotherapy (98.9%) followed by HDCT and ASCT (46.7%).

3.2.5 Perspective, time horizon and discounting

The perspective follows NICE methods guide recommendations. The time horizon is 50 years and costs, and health outcomes were discounted at a discount rate of 3.5% per annum. The EAG disagrees with the annual application of a discount rate during the weekly cycle period of the economic model used in the company base case and prefers a per cycle discount rate for this period instead.

3.2.6 Treatment effectiveness and extrapolation

To inform their partitioned survival model health states, the company extrapolate data from the EFS and OS outcomes from the TRANSFORM trial. A consequence of using the EFS outcome is that the post-event population is heterogeneous as some patients in this group will be cured at third line, whilst others will not. Hence, the EAG does not consider it appropriate to refer to this post-event group as a "health-state". This approach is highly likely to underestimate the total QALYs for SOC as it those cured at 3rd line are modelled to have a lower quality of life than those cured at 2nd line.

The EAG prefers to instead use the PFS2 outcome to inform the model health-states, which the company implemented in the model in response the EAG's request (clarification B3). Patients experiencing a PFS2 event are unlikely to be cured, whilst those without a PFS2 event are likely to be cured. The EAG considers that this division is more distinct and makes for better defined health-states.

All outcomes are extrapolated using mixture cure model versions of standard parametric models. The EAG accepts the rationale for using these models which assume a cure, as this is consistent with the intention and data for CAR T therapies, and has been used in other technology appraisals of similar technologies. The output from the mixture cure models fitted by the company report a cure-proportion, that is a proportion who are not at risk of the event. This can be helpful when distinguishing between different models, but relies on data being sufficiently mature to produce an accurate estimate of this proportion.

3.2.6.1 Event free survival

The company extrapolate EFS data from both arms of TRANSFORM. The company report that the assumption of proportional hazard rates between arms did not hold and so extrapolated each arm separately using a set of candidate mixture cure models. The model does not apply background mortality to EFS meaning the EFS extrapolations eventually cross the OS extrapolations.

For liso-cel, the company rule out generalised gamma and Gompertz models based on their interpretation of clinical expert input from TA895, where it was noted that relapses were likely to occur within the first two years. As these models predicted that over 10% of the non-cured population would still be event-free at 2 years, the company deemed these models implausible. The EAG is not clear how the company has arrived at the 10% threshold it has applied, and does not consider this strong justification for ruling out these models. The EAG notes that these two models produce the most pessimistic predictions for EFS of liso-cel, whilst all other models produce almost identical predictions (Figure 29 of Company Submission).

From the remaining models, the company opted for the log-normal model based on its goodness of fit statistics.

Whilst the EAG does not support using EFS outcome in the economic modelling, it has a preference for the generalised gamma model, as this has the best statistical goodness of fit, and produces a cure fraction that is most consistent with long-term follow-up for axi-cel in ZUMA 7, which has an EFS rate of 39% at 4 years.[43]

For SOC, the company notes the all the models produced very similar predictions (Figure 33 of Company Submission). The company select the log-normal model as it was consistent with their preferred extrapolation for liso-cel and was the model with the second-best goodness-of-fit statistics. The company also considers the generalised gamma as plausible as it had the best goodness-of-fit statistics. The EAG prefers the generalised gamma distribution, for consistency with its preferred extrapolation for EFS of liso-cel, but accept the log-normal model as plausible.

3.2.6.2 Progression free survival on second therapy (PFS2)

As stated earlier, the preference of the EAG is to instead use the PFS2 outcome to inform the model health states. Information on the extrapolation of this outcome was provided in the company clarification responses (B3 and Appendix B).

Whilst the company prefer not to use this approach, they still present their preferred set of models for this outcome for liso-cel and SOC. A limitation of the information provided was that it omitted details on censoring and the number of people at risk. The EAG considers that there is still considerable uncertainty over the cure rates for this outcome, and hence also for overall survival.

As with EFS, the company model does not apply background mortality of PFS2, meaning it will converge with the OS extrapolation at some point.

For liso-cel, following a similar algorithm to selecting a preferred model to EFS, the company select a log-logistic model, which estimates a cure fraction of [redacted]. The EAG accepts the company's choice as plausible, however the EAG prefers to use the Weibull model as the associated cure rate ([redacted]%) is most consistent with the 5 year overall survival rate observed in ZUMA-7 (~52%).[43] The EAG expect the PFS2 and OS extrapolations would converge between 5-10 years, with minimal or no occupancy of the post-PFS2 health state beyond this point as people are unlikely to be alive if they have not been cured. The Weibull does have slightly inferior goodness-of-fit statistics, however the differences are not considered important.

For SOC, the company rule out the generalised gamma and exponential model based on their implausible predictions for non-cured patients. From the remaining models, the company selects the log-normal model based on goodness-of-fit statistics.

The EAG compares the model predictions to long-term follow-up from ZUMA-1, where axi-cel is used in 3rd line setting.[44] Whilst not all patients will receive CAR T at 3rd line, the EAG anticipates that most will receive it as it has a positive recommendation from NICE. The EAG's clinical experts advised that ~10-20% of patients may instead receive palliative care. Whilst the true cure proportion for this population is unknown, the EAG considers both the log-normal and the log-logistics models as plausible, as their cure rates ([redacted]) are consistent with the 5 year OS rate reported from ZUMA-1 of 42.6%, which when scaled down to apply to the

80-90% of the population comes gives a range of (34.08%, 38.34%). The EAG select the log-logistic model for their base-case analysis.

3.2.6.3 Overall survival

For this outcome, again the company extrapolate data from both arms of TRANSFORM. Mixture cure models are fitted separately to each arm, and no assumption of proportionality is made. The company assessed whether such an assumption was appropriate and found it was not violated, however the company still opted for independent modelling of both arms for consistency with their EFS modelling. For all patients considered cured, the company apply a standardised mortality ratio of 1.09 to general population background mortality, which is obtained by Maurer et al. (2014) and is consistent with other similar appraisals. The EAG is content with this approach to modelling.[45]

The EAG considers the OS data less mature than the EFS and PFS2, as fewer events have been observed, and it is less likely that the true cure proportion is being estimated accurately. This is support by simulation studies by Kearns *et al*. and Grant *et al*. who showed that cure models fitted to short follow-up consistently overestimated the cure proportion.[46, 47] The EAG also notes that the OS follow-up from TRANSFORM is less mature than that of ZUMA-7, in addition to the much smaller sample size of TRANSFORM. Hence the EAG considers ZUMA-7 a more reliable for source for estimating long-term efficacy.

For both arms of TRANSFORM, the company consider the visual fit, the plausibility of extrapolations, the predicted survival of non-cured patients, the cure proportion and goodness of fit statistics.

For liso-cel, the company opt for the log-normal mixture cure model, having ruled out the exponential and Gompertz for poor visual fit, and ruling out the Weibull and Gamma due to their low prediction of 4 year survival for non-cured patients. Of the remaining extrapolations, the log-normal was the model that produced a cure-fraction (60.3) closest to predictions made by their clinical experts. The company report in their text that the range of the most plausible cure proportions predicted by their experts was [redacted], however Table 40 of the company submission shows the

mean values of the lower and upper plausible values were [redacted] respectively.

The EAG considers the company's preferred model to be too optimistic, as the OS cure rate is much higher than is predicted by the models fitted to PFS2 data. The EAG anticipates the PFS2 outcome to be highly predictive of OS and has the benefit of observing more events than OS within the current follow-up. The EAG is not aware of justification to support such a large difference based on the company's preferred models for each outcome (60.3% vs [redacted])

The EAG also compared extrapolations from this appraisal to predictions for axi-cel (TA895), another CAR T therapy. A key difference between TA895 and this current appraisal is that 3rd line CAR T (axi-cel) is now recommended, whereas it was previously only available through the CDF and so it was not accounted for in the economic modelling for the SOC arm in TA895. However, the CAR T arms are unaffected by this change and so the data and assumptions are more generalisable across the treatments and trials. The EAG notes that in TA895, a generalised gamma and log-logistic extrapolation were both considered plausible by the committee. Whilst the exact cure proportions from these models are not publicly available, the EAG estimates these to fall between 40% and 50% from visual inspection of the extrapolations (Figure 4).

The EAG compares observed and predicted time-to-event outcomes from follow-up of 2L axi-cel and liso-cel (

Table 21). The EAG notes that across outcomes, that liso-cel shows short term benefit compared to axi-cel, however the benefit appears to reduce as follow-up increases. This could be attributed to the more favourable safety profile of liso-cel compared to axi-cel, and the EAG do not consider the evidence strong enough to support a long-term benefit. The EAG sought to compare the duration of response outcome across trials, to inform on potential differences in long-term efficacy, however this was not possible as median follow-up was 33.9 months in TRANSFORM and the median DOR was not observed, whilst median DOR in ZUMA-1 was 41.7 months.[43]

Even the most pessimistic extrapolation of OS from TRANSFORM (exponential) predicts a higher long-term survival rate than what was accepted in TA895.

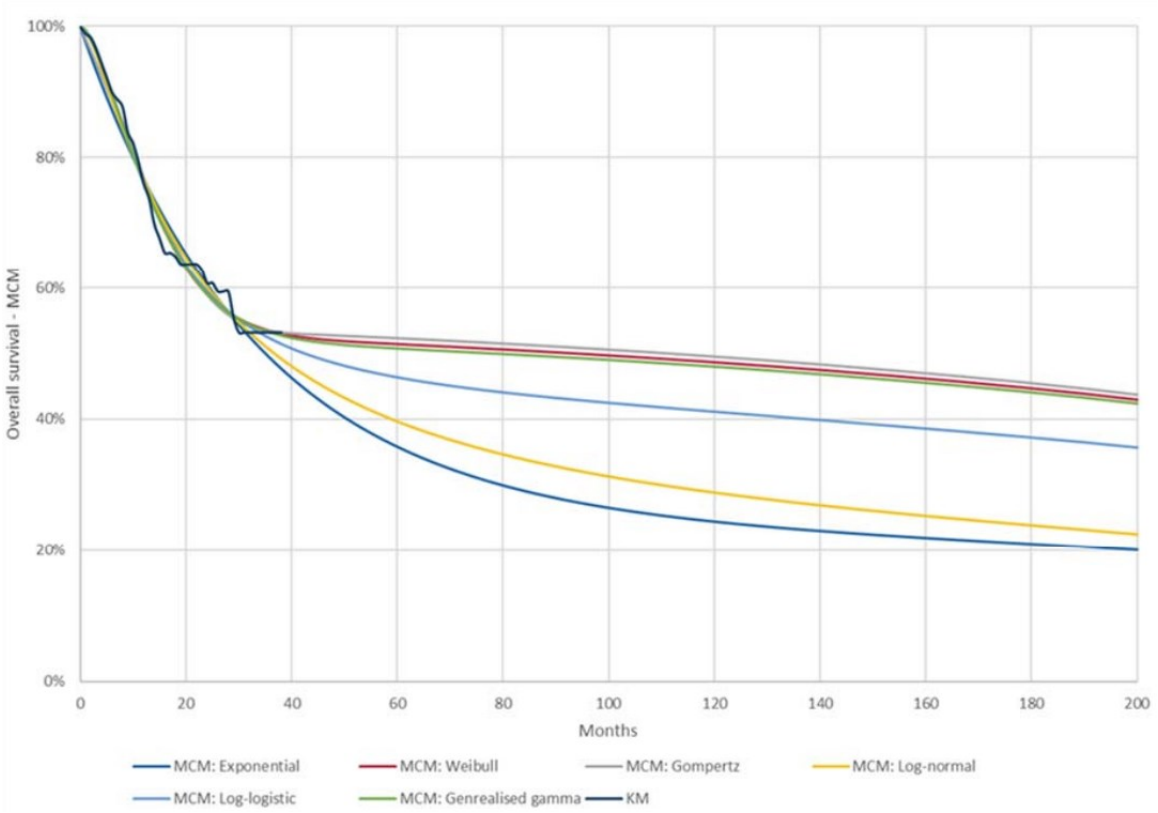

Figure 4: Extrapolations of axi-cel taken from EAG Report of TA895, Figure 9.

Table 21: Comparison of overall survival related outcomes and predictions for liso-cel and axi-cel

	Axi-cel (ZUMA 7)	Liso-cel (TRANSFORM)	Difference
EFS:			
1 year	49%	[redacted]	[redacted]
2 year	44%		
3 year	41%	45.8%	4.8%
4 year	39%	N/A	-
OS:			
1 year	76%	83.5%	7.5%
2 year	60%	67.5%	7.5%
3 year	56%	62.8%	6.8%
4 year	55%	N/A	-
PFS:			
1 year	52%	63.0%	11.0%
2 year	46%	57.0%	11.0%
3 year	44%	50.9%	6.9%
4 year	41%	N/A	-
Predicted OS:	GenGam / Log-log	Log-norm / Exponential	
5 year	50.5% / 46.2%*	59.4% / 57.5%	-
10 year	47.7% / 41.1%*	54.0% / 50.2%	-
15 year	43.8% / 37.0%*	48.5% / 44.8%	-

*Estimated from EAG digitization from TA895 committee papers.

The EAG identified a real-world study which compared outcomes for people who received liso-cel or axi-cel.[48] This abstract by Portuguese *et al*. did not show any clear OS benefit for liso-cel (Figure 5). In addition, two published indirect comparisons comparing 3L axi-cel and liso-cel found that axi-cel was associated with a significant OS benefit (HR = 0.53, 95% CI = 0.34-0.82; HR = 0.54, 95% CI = 0.37, 0.79).[49, 50]

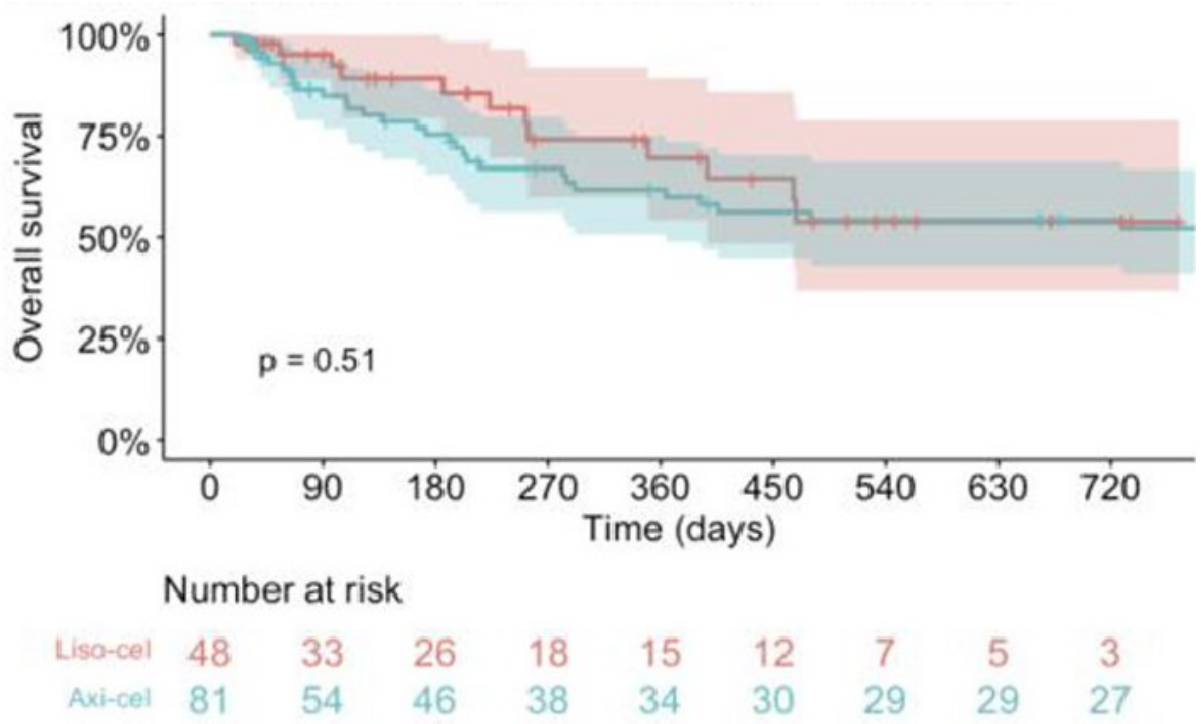

Figure 5: Real world overall survival of liso-cel and axi-cel (taken from Figure 2 of Portuguese et al.)

The results of the company's preferred selection of models for liso-cel EFS and OS are shown in Figure 6. The company assumptions show a crossing of EFS and OS curves for liso-cel from roughly 18 years. Beyond this point, there are no people remaining the post-EFS event health state. The EAG finds this implausible as there is a potential for curative ASCT being received at third line for a small number of people.

[redacted]

Figure 6: EFS and OS curves from company's preferred modelling for liso-cel.

For these reasons, the EAG conclude that the large OS benefit modelled for liso-cel by the company to be implausible and inconsistent with currently available information.

Instead, the EAG uses SurvInt, a freely available tool which can be used when standard modelling approaches fail to provide a plausible extrapolation.[51] The EAG aimed to obtain a model that is consistent with the early follow-up from TRANSFORM, the long-term follow-up of ZUMA-7 and also the cure rate for PFS2. The inputs for SurvInt were as follows:

[t1, S(t1)] = [11.05,0.85] - taken from TRANSFORM

[t2, S(t2)] = [48.00, 0.55] - taken from 4-year follow-up from ZUMA-7

Cure proportion = 0.50 - estimated for consistency with cure proportions of PFS2 and extrapolations from ZUMA-7

The EAG selected a log-logistic model as this was the most visually consistent with the TRANSFORM data. This model is also consistent with the company's rule for selecting a model which predicts <10% of non-cured people are alive at 4 years (9.97%).

A visual representation of the EAG's preferred log-logistic model using SurvInt is shown in Figure 7, compared to digitised TRANSFORM data. It deviates from the TRANSFORM data when in the tail when there is a high rate of censoring, and is instead consistent with the ZUMA-7 observed data (not shown).

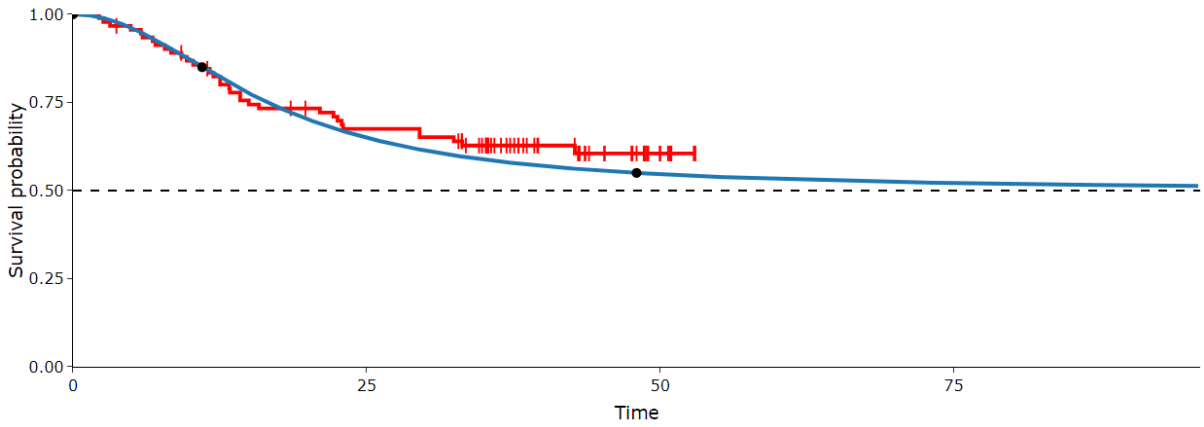

Figure 7: EAG preferred log-logistic extrapolation for liso-cel obtained using SurvInt

The resulting Markov Trace for the EAG's preferred assumptions is shown in Figure 8. The population of the post-PFS2 event remains small and is zero beyond roughly 6 years.

Figure 8: PFS2 and OS curves for liso-cel from EAG preferred assumptions

For SOC, the company select a log-normal model based on statistical goodness-of-fit, despite acknowledging that all candidate models likely overestimated long-term survival. The cure proportions ranged from 50-55% which were outside the range predicted by their clinical experts ([redacted]%) The EAG agrees that due to the immaturity of the data, it is likely that the cure proportion is overestimated by all models.

The combined company assumptions for EFS and OS result in the modelling that there are no people remaining in the post-EFS-event health-state beyond 30 years (Figure 9). The EAG considers this implausible, as there are likely to be some individuals cured by 3rd line CAR T in this group.

Figure 9: EFS and OS curves from company's preferred modelling for SOC.

The company conducted a scenario analysis where they fitted models separately to the SOC arm of TRANSFORM and to the CORAL study, which included patients using SOC without the influence of 3L CAR T therapy. They then combined these models using a 66.25% weight for the TRANSFORM extrapolation, and 33.75% weight for the CORAL extrapolation, however it is not clear how these percentages were obtained and they do not seem to account for the proportion of the TRANSFORM SOC population who did not receive subsequent CAR T. Hence, the EAG does not consider the methodology of this approach robust.

In the absence of alternative options, the EAG preference is to use SurvInt to obtain a plausible extrapolation for SOC. As the SOC arm from ZUMA-7 was not a suitable reference, all inputs to SurvInt came from TRANSFORM:

[t1, S(t1)] = [6.59,0.86] - taken from TRANSFORM

[t2, S(t2)] = [17.76, 0.63] - taken from TRANSFORM

Cure proportion = 0.35 - estimated for consistency with cure proportions of PFS2

Whilst this model underestimates the tail of the Kaplan-Meier curve from TRANSFORM, the EAG considers this may be an appropriate deviation given the faster access to 3L CAR T that occurred in the trial compared with real world practice and the other differences between 3L+ treatments received in TRANSFORM compared with real-world NHS care (section 3.2.8.3). Whilst the percentage of uncured patients remaining alive at 4 years is just above the company's 10%

threshold, the EAG considers that a difference here between arms may be reflective of the potential greater efficacy of 3L+ therapies in a CAR T naïve population as hypothesized by their clinical experts, but also that the company's threshold is somewhat arbitrary.

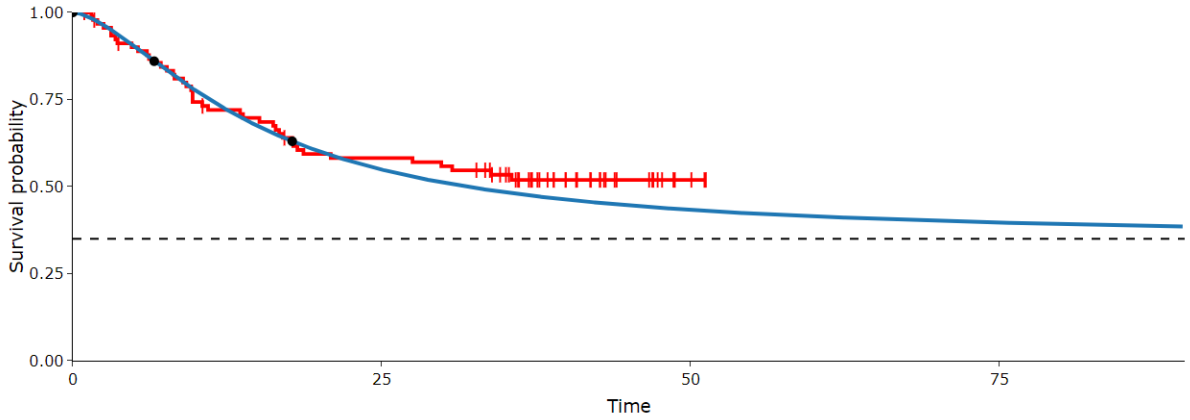

Figure 10: EAG preferred log-logistic extrapolation for SOC obtained using SurvInt

The EAG's preferred curves resulting Markov trace can be seen in Figure 11. The PFS2 and OS curves cross at roughly 6 years, beyond which the post-PFS2 event health state is zero.

[redacted]

Figure 11: PFS2 and OS curves for SOC from EAG preferred assumptions

3.2.6.4 Time to next treatment

The company extrapolate time-to-next treatment data from the TRANSFORM trial to inform the modelling of subsequent treatments.

A TTNT event included death or starting a subsequent treatment. Hence, after estimating the TTNT curve, the company then apply a multiplier, scaling down the incidences of beginning new treatment, based on the proportion of new-treatment events out of all TTNT events.

At 5 years, the company assumed that no new TTNT events would occur related to the primary disease, and did not capture any subsequent treatment costs beyond this point.

For liso-cel, the company select a log-normal extrapolation, as this has the best AIC and BIC after excluding the generalised gamma model as it predicted >10% of non-cured patients to have not had a TTNT event at 2 years.

The EAG is unclear why there is disagreement between the EFS and TTNT liso-cel outcomes, with the TTNT extrapolations more optimistic, in particular given their similarity in descriptions. Whilst censoring information on TTNT is not provided, the EAG considers that the EFS outcome will be more mature, and likely to give a more reliable long-term extrapolation. EFS is also provided with information on censoring to support a more informed choice over the plausibility of the cure proportion. The EAG also note that the TTNT extrapolations are more optimistic than those published in TA895.

The EAG prefers to use the generalised gamma EFS extrapolation from TRANSFORM to model TTNT. This model is consistent with the EAG preferred OS extrapolation, allowing for some people to be cured by subsequent ASCT, and is also consistent with the TTNT rate from the TA895.

Table 22: Comparison of 5 year rates for TTNT-free for CAR T therapy.

	5 year TTNT liso-cel	5 year EFS liso-cel	5 year range from TA895 CAR T
Exponential	[redacted]	[redacted]	40.6% - 43.0%
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Gen Gamma			
Gamma			

For SOC, the candidate extrapolations of TTNT from TRANSFORM showed strong similarity. The company opted for the log-normal model for consistency with their choice of model for liso-cel and on statistical goodness-of-fit. The EAG prefer again to use an EFS extrapolation to inform TTNT, and opt for the log-normal model as it was an acceptable EFS model, and produces a 5 year estimate similar to what was modelled for SOC in TA895.

Table 23: Comparison of 5 year rates for TTNT-free for SOC.

	5 year TTNT SOC	5 year EFS SOC	5 year range from TA895 SOC
Exponential	[redacted]	[redacted]	19.7% - 20.7%
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Gen Gamma			
Gamma			

3.2.7 Health related quality of life

EQ-5D-5L was collected in the TRANSFORM trial. Out of the 184 patients in TRANSFORM, [redacted] were included in the EQ-5D analysis set. EQ-5D-5L data were mapped to the 3L using mapping function developed by Hernandez *et al*.[52]

A regression model was fit to the data adjusting for baseline utility (centred at the mean value of the EQ-5D evaluable population), liso-cel pretreatment, EFS status and grade 3 AE. Treatment independent utility values were used in the CEM for event-free and post-event health state.

AE disutility was estimated using multi-variate model adjusted for EFS events, Grade ≥ AEs, and lymphodepleting chemotherapy. Utility decrement derived from TRANSFORM were applied to all Grade ≥3 AEs and hypogammaglobulinemia for the average AE duration in TRANSFORM ([redacted]). Disutilities for CRS and neurotoxicity were derived from TA895. Lymphodepleting chemotherapy was associated with a disutility of [redacted] and applied for 3 days based on TRANSFORM data.

Table 25 summarises the disutility estimate used in the model and the duration the AE were applied.

Patients who remain progression and event-free after 5 years are assumed to revert to general population utility levels.

Table 24: Summary of Grade ≥3 AE disutilities included in the economic model

AE	Utility decrement (SE)	Utility decrement source	Duration of AE (days)	Duration source
CRS	0.852	As per approach in TA895[53]	8.3	TA895[53]
Neurotoxicity	0.150	TA895[53]	40	TA895[53]
Hypogammaglobulinemia	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H [54]	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H[54]
Neutropenia				
Thrombocytopenia				
Anaemia				
Lymphopenia				
Febrile neutropenia				
Hypophosphatemia				
Leukopenia				
Prolonged cytopenia				
Infections				
Hypertension				

The company implanted a scenario where PFS-2 were used rather than EFS. Utility for the post-PFS-2 health state were obtained from TA895, which used data from ZUMA-1.

Table 25 summarises the utility values used for the PFS-2 state, EFS, post-event and post-progression health state.

Table 25 Summary of health-state utility values used in the base case economic analysis and PFS-2 scenario analysis

Health state	Utility (Mean)	Source
Event-free	0.852*	TRANSFORM EQ-5D analysis (final DCO; October 2023)
Long-term remission	0.853*	
Post-event	0.808*	
Pre PFS-2 event	0.852	TRANSFORM UK Utility analysis, 23 Oct 2023 DCO
Post PFS-2	0.72	Post progression utility value TA895, ZUMA-1 3L axi-cel
Long-term remission	0.853	TA895 final utilities (EFS: ZUMA-7, PD: 3L axi-cel trial)

*used in company base case

The EAG considers that utility and AE disutility were applied appropriately. However, the utility for the overall population who remain event-free and progression-free is too optimistic. The estimate used for event and progression-free population differs significantly from estimates used in previous appraisals. For example, in TA985, the committee accepted a utility value of 0.785 for patients who remain event-free at 2L. Indeed, the estimate used in the company base case is similar to general population utility levels (0.852 used in the company base case compared to general population utility estimate of 0.853; disutility of -0.001).

The EAG prefers a utility value of 0.785 for the overall population who are progression-free and event-free for the period where patients may be unwell and face uncertainty over their prognosis. After 5 years, the proportion of cohort who remain free of an event revert to general population utility levels. This approach is similar to the approach taken in TA895 and appropriately applies a significant utility benefit for the population cohort who are cured.

3.2.8 Resources and costs

Intervention and comparator costs were applied separately for each arm. Costs were considered from an NHS and PSS perspective. Resource use and costs are summarised across the following sections.

3.2.8.1 Intervention costs

The main costs associated with liso-cel consist of the CAR T tariff, bridging therapy costs and liso-cel drug acquisition costs. In this document, the EAG used costs as provided by the company. Prices used in the confidential appendix can be found in appendix 4 of this report.

3.2.8.1.1 CAR T tariff costs

CAR T tariff costs were assumed to include all costs associated with a decision to have CAR T until 100 days after infusion. The CAR T tariff costs include the following categories:

- **Pre-treatment:** Leukapheresis and lymphodepleting chemotherapy
- **Treatment:** Liso-cel drug administration costs
- **Post liso-cel infusion:** Resource use and AE management costs up to 100 days after infusion

The CAR T tariff costs notably cover the cost of all treatment-related AEs except for treatment of hypogammaglobulinemia. A single CAR T tariff cost of £41,101 was applied in line with NICE TA895. The company commented that this likely overestimates the costs associated with liso-cel as they were calculated based on axi-cel which is associated with more CAR T related AEs. The EAG accept this point however is unable to comment on the magnitude of the impact as the breakdown of the calculation is not reported.

For patients who discontinued treatment prior to receiving lymphodepleting chemotherapy, they were assumed to incur costs of leukapheresis and bridging therapy only. Patients who received non-conforming product were assumed to incur CAR T tariff costs and administration costs. Drug acquisition costs were not applied.

The patient flow during CAR T pre-treatment period is summarised in

Table 26.

Table 26 Patient flow during liso-cel pre-treatment period

	Liso-cel (TRANSFORM final DCO; October 2023)
Patients who undergo leukapheresis but do not receive CAR T infusion	2.17%
Patients who die prior to CAR T infusion	0.00%
Patients who receive planned treatment	96.74%
Patients who receive an out-of-specification CAR T product	1.09%
Total	100%

3.2.8.1.2 Bridging therapy costs

Bridging therapies were aligned with the TRANSFORM trial and included R-GDP, R-DHAP and R-ICE. The proportion of patients receiving bridging therapy was in the company base case was based on the TRANSFORM trial where 63% of patients received bridging therapy. Bridging radiotherapy was not included in the company base case but were considered in a scenario analysis alongside other novel therapies not included in the company base case based on clinical expert estimates. Bridging therapy costs were applied to patients receiving 3L CAR T therapy and assumed equivalent to the proportion of participants receiving liso-cel. Bridging therapy drug acquisition costs and the proportion receiving each regimen are outlined in CS Table 54.

Administration costs were applied to bridging therapy excluding oral therapies. The administration of R-DHAP included the cost of two days of inpatient administration while the administration of R-ICE included the cost of three days of inpatient administration. A maximum of one administration cost was applied per day for inpatient treatments. Administration costs applied in the model are detailed in CS Table 55.

The EAG has concerns regarding the costs applied in the company base case. The company base case assumes equivalence between the proportion and distribution of patients who received bridging therapy at 2L prior to liso-cel infusion with those in the SOC group who receive 3L CAR T. However, the bridging therapy used prior to liso-cel infusion at 2L (R-GDP, R-DHAP and R-ICE) were re-induction chemotherapies given to 2L SOC. Using the same bridging therapy at 3L CAR T does not consider the possibility that patients unresponsive to chemotherapy at 2L may are given the same therapy as bridging therapy at 3L. Unlike UK clinical

practice, bridging therapy distinct to the regimens received as part of the SOC intervention was not given to participants in the SOC group. Clinical experts consulted by the EAG suggested that the proportion of patients receiving bridging therapies and the distribution of bridging therapies will differ from those currently modelled in the company base case. In a study of CAR T use in the UK, Boyle *et al*. reported that 11% of CAR T patients received no bridging therapy or steroids.[55] Hence the EAG prefers to model that 89% patients receiving CAR T therapy will require bridging therapy rather than 63% in the company base case. The EAG also prefers to use the distribution of bridging therapies taken from Boyle *et al.*[55] Table 27 compares the preferred assumptions relating to bridging therapy by the company and EAG.

Table 27: Comparison of assumptions relating to bridging therapy associated with CAR T

	Proportion Receiving Bridging Therapy	R GDP	R DHAP	R ICE	PolaBR	Radiotherapy
Company Bridging Assumptions	63.04%	[redacted]	[redacted]	[redacted]	0.00%	0.00%
EAG Bridging Assumptions	89.00%	6.74%	6.74%	6.74%	64.04%	35.96%

3.2.8.1.3 Liso-cel acquisition costs

Liso-cel is administered as a single infusion with a list price of £297,000. A single PAS discount of [redacted] is applied to the list price of liso-cel and a cost of [redacted] applied in all analyses.

3.2.8.2 SOC costs

SOC costs were based on drug acquisition and administration costs associated with re-induction chemotherapy, HDCT and ASCT. 1/92 patients who did not receive SOC were assumed to not incur SOC acquisition costs but received subsequent therapy costs in the SOC arm.

3.2.8.2.1 Reinduction chemotherapy

Patients were modelled to receive R-GDP, R-DHAP and R-ICE as re-induction chemotherapies, in line with the TRANSFORM trial (final DCO; October 2023). All chemotherapy regimens were assumed to be delivered in in-patient settings except R-GDP. CS Table 56 presents a breakdown of costs associated with chemotherapy.

3.2.8.2.2 HDCT and ASCT

43/92 patients (46.7%) received HDCT and ASCT following immunochemotherapy. HDCT was assumed to include BEAM regimen. Administrative costs of BEAM were assumed to be included in the costs of ASCT. The drug acquisition and administrative costs of BEAM and ASCT are presented in CS Tables 56 and 57.

3.2.8.3 Subsequent treatment costs

Costs associated with subsequent treatment were applied as a one-off cost based on TTNT data from TRANSFORM trial. The company calculated what proportion of TTNT events were the initiation of new therapy, as opposed to death, and applied this to the TTNT extrapolation. For more information see CS Table 58. The resulting assumption was that 69.6% of liso-cel patients and 94.2% of SOC patients experiencing a TTNT event would receive a subsequent therapy. The EAG's clinical experts did not consider the SOC rate to be plausible of clinical practice and is inflated due to the design of the trial. They estimated that in practice roughly a third of patients would move to palliative care following an unsuccessful attempt at 2L ASCT. Hence the EAG modelled that 66% of SOC patients experiencing a TTNT event would receive subsequent therapy, which is plausibly similar but slightly lower than what was modelled for liso-cel, which the EAG did not change.

The distribution of subsequent therapies applied the company came from TRANSFORM. The EAG compares this to estimates from the company's clinical experts in Table 28. The EAGs clinical experts suggested values consistent with the company's experts' estimates, and so the EAG opt to use these estimates in their base case.

For 3L+ chemotherapy, patients were assumed to receive 100% R-Bendamustine in an outpatient setting. Only drug acquisition costs and administration costs were considered at 3L+. AE costs were not considered.

Patients receiving CAR T therapy at 3L+ were assumed to incur CAR T tariff costs, bridging therapy costs and drug acquisition costs of axi-cel (at list price: £280,451)

The EAG considers the subsequent treatment distribution of novel therapies used in TRANSFORM and thus the company base case not reflective of UK practice. Based on data received from NHS England, the EAG prefers to use estimates from the clinical experts consulted by the company for both subsequent therapy options and for the breakdown of novel therapies, as outlined in Table 28.

Table 28: Subsequent treatment proportions for those who receive subsequent treatment

Subsequent treatment option	TRANSFORM Liso-cel	Expert Liso-cel	TRANSFORM SOC	Expert SOC
ASCT	9.38%	1.25%	0.00%	1.25%
Allo-SCT	25.00%	3.75%	3.08%	3.00%
3L+ chemotherapy	100.00%	15.00%	35.38%	11.75%
Other novel therapy	0.00%	81.25%	0.00%	54.75%
3L+ CAR T	0.00%	0.00%	93.85%	66.25%
3L+ radiotherapy	12.50%	0.00%	0.00%	11.75%
Other novel therapy breakdown	PolaBR	Glofitamab	Lon-Tes	Epcoritamab
Company expert estimates – liso-cel (not used by company due to 0% above)	12.3%	40.0%	7.7%	40.0%
NHS England – liso-cel*	0/44 (0%)	35/44 (80%)	2/44 (4%)	7/44 (16%)
Company expert estimates – SOC (not used by company due to 0% above)	16.9%	36.5%	10.0%	36.5%
NHS England – SOC**	0/225 (0%)	157/225 (70%)	33/225 (15%)	35/225 (15%)

* based on data for people receiving treatment after no prior CAR T or 3L CAR T.
** based on data for people receiving treatment after 2L CAR T.

Pola: presumed not used due to earlier line use; Glo range: 07/09/2023 – 17/07/2024 plus 16 prior EAMS patients; Lon range: 17/12/2023 – 17/07/2024; Epco range: 01/02/2024 – 17/07/2024

3.2.8.4 Health state costs and resource use

Health state resource use was applied based on clinical experts consulted by the company. CS Table 63 and 64 details a breakdown of the health state resources and costs applied in the model. The EAG considers the resource use unit costs were appropriately sourced.

3.2.8.5 Adverse event costs and resource use

AE costs were applied separately for each arm based on incidence reported in the TRANSFORM trial.

For liso-cel, AE costs were assumed to be included in the CAR T tariff costs with the exclusion of costs associated with the management of hypogammaglobulinaemia.

For SOC, costs were applied for all Grade $\geq$ 3 AEs that occurred in >5% of patients.and all grade AESI namely CRS, neurotoxicity and hypogammaglobulinaemia. Costs included in the model for the management of AEs in the SOC arm are outlined in CS Table 65.

Costs associated with neurotoxicity events were granularly applied in the SOC group. A breakdown of the cost associated with the management of neurotoxicity is outlined in CS Table 66, whilst costs associated with managing hypogammaglobulinaemia are in CS Table 67.

The company does not apply AE costs at 2L liso-cel with the assumption that such costs are covered by CAR T tariff. Indeed, as reported in Section 3.2.8.1.1 CAR T tariff include pre-treatment costs, treatment administrative costs and post-infusion costs including AEs occurring 100 days after infusion. In effect, this excludes adverse events occurring beyond this point from being included in the model. However, for SOC CAR T tariffs were applied to patients receiving CAR T at 3L, in addition to the modelling of AE costs that occurred as observed within the trial follow-up. The EAG considers this may be double counting AEs for SOC, whilst underrepresenting them for liso-cel.

Given the implicit assumption that AE costs are not accounted at 3L+, applying the full costs of CAR T with no adjustments for excluding AEs biases the ICER in favour of liso-cel. From the CEM submitted by the company, the £41,010 CAR T tariff applied in the base case includes an estimated AE cost of £10,611. The EAG argues this cost should not be included in the CAR T tariff at 3L+ patients receiving CAR T to align with the company base case assumption of not including AE costs at 3L for liso-cel, and thus excludes this cost in the EAG base case.

3.2.8.6 End of life care costs

Patients who died in the CEM within 5 years are assumed to incur end of life care costs of £10,687 based on PSSRU hospital care estimates (2022). Those who survived beyond 5 years are assumed to incur no costs.

3.3 *Severity modifier*

No severity modifier was applied in the company base case, and the EAG agree with this conclusion.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

Under the company's base case assumptions, liso-cel dominated SOC with a cost reduction of [redacted] and incremental QALY of [redacted]. The company deterministic base case cost-effectiveness results are presented in Table 29.

Table 29: Company base case deterministic results

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NHB at £20,000/ QALY	NHB at £30,000/ QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	[redacted]	-				

4.2 *Company's sensitivity analyses*

The company conducted a series of deterministic sensitivity analyses to explore which parameters were most influential on the ICER. Those most influential were the proportion receiving subsequent treatment in SOC arm, and those receiving subsequent CAR T (see CS Figure 56).

The company also conducted probabilistic sensitivity analyses (PSA) by simultaneously varying different model parameters in a Monte Carlo simulation to explore the impact of parameter uncertainty on their base case. The conclusions of the base case were unchanged. Liso-cel was associated with a cost reduction of [redacted] and incremental QALYs of [redacted] compared to SOC. The company probabilistic base case cost-effectiveness results are presented in Table 30. Visual representation of the PSA can be found in CS Figures 54-55.

Table 30: Probabilistic base-case results

	Total costs	Total QALY	Incremental Costs	Incremental QALYs	ICER	NHB at £20,000/ QALY	NHB at £30,000/ QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]				

The company also undertook a series of scenario analyses, exploring the impact of alternative assumptions and inputs on the cost-effectiveness results. None of the scenarios changed the conclusions of the base case. There is only in one scenario using alternative distributions for subsequent therapies, and alternative OS extrapolations where the incremental costs get relatively close to zero, however liso-cel remains dominant. Detailed results can be found in CS Table 79.

4.2.1 Company PFS2 Implementation

Following the EAG's request to explore using PFS2 in the economic model, the presented a preferred analyses based on this approach to modelling. Resource use was based on EFS curve while health outcomes were based on the PFS-2 curve. The company deterministic and probabilistic base case results from this scenario is presented in Table 31 and Table 32 below.

Table 31: Deterministic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	Dominant	2.65
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.59

Table 32: Probabilistic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	Dominant	2.51
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.55

4.3 *Model validation and face validity check*

The EAG conducted validation checks on the model and it appears to reflect the modelling reported in the company submission.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *Exploratory and sensitivity analyses undertaken by the EAG*

5.1.1 Exploratory Analyses

The EAG undertook a series of analyses to explore the impact of their preferred changes to the company base case.

EAG01: Pre-event health state changed from EFS to PFS-2 to better represent the health states of this disease. (Section 3.2.2 and 3.2.6)

EAG02: Weibull distribution used for liso-cel PFS-2 and the loglogistic distribution used for SOC PFS-2 based on reasons outlined in Section 3.2.6.2.

EAG03: Discount applied per weekly cycle for first 5 years of model, rather than annually (Section 3.2.5)

EAG04: Using the log-logistic distribution for liso-cel OS and SOC OS where parameter estimates have come from methods outlined in Section 3.2.6.3.

EAG05: Generalised gamma EFS distribution is assumed for liso-cel TTNT and log-normal distribution is assumed for SOC TTNT where parameters for the chosen distribution is re-estimated following methods outlined in Section 3.2.6.4

EAG06: Bridging therapy changed to better reflect UK practice as detailed in Section 3.2.8.1.2.

EAG07: Adverse events costs removed for 3L CAR T in SOC group for consistency as discussed in Section 3.2.8.5.

EAG08: Subsequent therapy distributions changed to better reflect UK practice as outlined in Section 3.2.8.3

EAG09: Utility values changed from company base case (0.852) to estimates used in NICE TA895 (0.785) as discussed in Section 3.2.7.

EAG10: Starting age of the model changed from [redacted] to 59 to align with the starting age used in NICE TA895 and current data for 2L axi-cel use in CDF.

The individual and cumulative effect of these changes is presented in

Table 33.

Table 33: Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Assumption	Reported section	ICER(£/QALY)
Company base case	N/A	-£29,314 (SOC dominated)
EAG01: Use PFS2 for model health state occupation	Section 3.2.2 and Section 3.2.6	-£30,589 (SOC dominated)
EAG02: Use Weibull and log-logistic PFS2 curves for liso-cel and SOC respectively.	Section 3.2.6.2	-£30,961 (SOC dominated)
EAG03: Discount applied per cycle.	Section 3.2.5	-£27,986 (SOC dominated)
EAG04: log-logistic parameters re-estimated and used for liso-cel & SOC OS	Section 3.2.6.3	-£23,149 (SOC dominated)
EAG05: log-normal and generalised gamma parameters re-estimated and used for SOC and liso-cel TTNT respectively	Section 3.2.6.4	-£36,540 (SOC dominated)
EAG06: Bridging therapy changed	Section 3.2.8.1.2	-£27,656 (SOC dominated)
EAG07: AE costs removed for 3L CAR T	Section 3.2.8.5	-£24,130 (SOC dominated)
EAG08: Subsequent therapy changed including proportion in SOC receiving CAR T at 3L	Section 3.2.8.3	£38,126
EAG09: Utility changed for pre-progression state	Section 3.2.7	-£26,078 (SOC dominated)
EAG10: Starting age of model changed	Section 3.2.3	-£31,806 (SOC dominated)
Cumulative		£38,638

5.2 *EAG's preferred assumptions*

The EAG base case deterministic result show an incremental cost [redacted] and QALYs of [redacted]. The ICER for the base case is £38,563. A more detailed summary of the base case is presented in Table 34 below.

Table 34: EAG Deterministic results (liso-cel PAS price)

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NMB at £20,000/QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	£38,638	[redacted]
SoC	[redacted]	[redacted]	-			

The EAG base case assumptions was subject to 500 iterations resulting in an incremental cost of [redacted] and QALYs of [redacted]. The probabilistic sensitivity analyses resulted in an ICER of £41,643.

Table 35 EAG Probabilistic results (liso-cel PAS price)

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NMB at £20,000/QALY WTP threshold
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	£41,812	[redacted]
SoC	[redacted]	[redacted]	-			

The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 12 and Figure 13, respectively.

Figure 12: Cost-effectiveness plane (EAG) liso-cel (PAS price) versus SOC

Figure 13: Cost-effectiveness acceptability curve (EAG): liso-cel (PAS price) versus SOC

5.3 *EAG additional analyses*

The EAG conducted a series of analyses building from their base case to explore the impact of the areas of key uncertainty. The following scenarios were explored:

Scenario 1: Vary proportion of patients receiving subsequent CAR T for SOC by 15% (i.e. +/- 15% around preferred clinician estimate of [redacted]%)

Scenario 2: starting age increased to 65 to explore the potential impact of an older liso-cel population.

Scenario 3: Proportion receiving other 3L novel treatment for in the SOC group varied by 15% (i.e. +/- 15% around preferred clinician estimate of [redacted]%)

Scenario 4: Exponential model used for liso-cel OS, as most plausible model fitted to liso-cel trial data.

All EAG base case assumptions were maintained unless affected by scenario explored. The results are shown in

Table 36.

Table 36: EAG scenario analyses

Scenario	Δ Cost	Δ QALYs	ICER
EAG Base Case	[redacted]	[redacted]	£38,638
Scenario 1 - Change Subsequent CAR T after 2L SOC	[redacted]	[redacted]	
+15% [redacted]			£24,357
-15% [redacted]			£52,920
Scenario 2 - Model age 65	[redacted]	[redacted]	£46,975
Scenario 3 Chance Subsequent Novel Therapies after 2L SOC	[redacted]	[redacted]	
+15% [redacted]			£34,635
-15% [redacted]			£42,642
Scenario 4 Exponential OS for liso-cel	[redacted]	[redacted]	£27,367

5.4 *Conclusions of the cost effectiveness section*

The company present a model that is consistent in structure with previous appraisals, however can be improved upon through the use of the PFS2 outcome instead of EFS. The company's analysis contains numerous inputs from the TRANSFORM trial which often come from insufficient follow-up and are not representative of UK care, distorting in particular the costs associated with SOC.

The EAG provides an analysis which it considers more reflective of UK practice, however considerable uncertainty remains over the impact on costs and efficacy of second line CAR T or SOC and the subsequent therapies received.

6 References

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7 Appendices

7.1 *Appendix 1: ROBIS assessment of the company SLR*

Table 37: EAG assessment of risk of bias of the CS systematic review of clinical effectiveness

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably no	The EAG are not aware of any pre-published protocol for the company SLR. The SLR was part of a wider review, there were changes made to searches and eligibility criteria at various updates and it is unclear if these were made *a priori* and whether excluded studies were rescreened according to new criteria. An additional set of criteria were used to select only the one relevant trial and this was not explicitly stated *a priori.* Furthermore, the company provided clarification [CQ A5] that studies were also excluded due to reasons not specified in

		the eligibility criteria. For example studies were excluded for 'other' reasons such as having few eligible patients, being protocols with no results, or not being relevant to the topic of the SLR.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The initial set of criteria presented in CS appendix Table 15 are appropriate for the wider review question. The criteria relevant to the decision problem were narrowed down in the CS to only include patients eligible for SCT with relapsed or refractory disease, compared with reinduction therapies R-DHAP, R-ICE and R-GDP. Therefore, this changed the CS inclusion to only one relevant trial from the SLR.
1.3 Were eligibility criteria unambiguous?	Probably yes	The eligibility criteria were generally unambiguous with the exception of the minimum sample size. The company's study design criteria require a minimum sample size by treatment arm (≥25 patients) or per study (≥50 patients). However, there's an inconsistency in how this criterion was applied. For

		example, a single-arm study with ≥26 patients was excluded because it does not meet the ≥50 patients per study criterion, even though it meets the ≥25 patients per treatment arm criterion. This inconsistency has the potential for studies being excluded inappropriately.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	CS appendix Table 15 specifies exclusion of articles published prior to 2003 and conference abstracts prior to 2017 with the rationale provided which appears appropriate. However, the reason for limiting sample size to 50 patients (25 per arm) is not provided, it is unclear whether this is appropriate
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No.	In the search, no language limits are applied. However, during screening only articles in English are included and all other languages excluded. While this may introduce bias of missing out articles in other languages, the restrictions are appropriate for this type of SLR.

Concerns regarding specification of study eligibility criteria	Unclear concern.	Effort has been made to clearly specify the review question and objectives. However, there is lack of clarity in how eligibility criteria were set and adhered to, particularly the EAG could not identify a pre-published protocol, changes to eligibility criteria, inconsistency in applying sample size criteria and potential language restrictions during screening suggest potential risks of bias.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes.	Searched Medline, Embase, Cochrane Central, proceedings of 8 named conferences, 3 trials registries and FDA and EMA websites (CS Appendix D.1.1.2).
2.2 Were methods additional to database searching used to identify relevant reports?	Probably Yes	Additional search methods were used such as grey literature searching and hand searches. Grey literature was sought and reported in Table 12 (CS Appendix D.1.1.2). The search terms are reported but the numbers of results retrieved are not reported in the search strategy, however the numbers reported to have been identified in the PRISMA-Flow diagram

		(CS Appendix D.2 Figure 1) signifies a comprehensive search. Additional searches of Medline, Embase, DARE and the Cochrane DSR were undertaken to identify systematic reviews and these reviews were hand-searched to identify further reports. Page 9 of the CS Appendix states 'Bibliographic handsearching of published SLRs for any further relevant records was also undertaken as part of the SLR'; however, full details of the supplementary searches or reviews, guidelines and grey literature examined are not reported.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No	The update searches (CS Appendix D.1.1.1 Tables 1-8) are sufficiently comprehensive and include terms for the population of interest only. A broad range of free text and database-specific terms were used for R/R/ DLBCL) and concepts related to refractory disease, such as drug resistance, non-response, treatment failure or salvage therapy were also included. Filters for observational and non-

		randomised controlled trials appear to be based on the CADTH search filters. The original search (CS Appendix D 1.1.1 Table 9 and 10) is substantially less sensitive and contains major flaws, for example, the limited selection of free text and thesaurus terms, errors in combining search lines, concepts related to refractory disease not being included and thesaurus (MeSH / Emtree) terms being rarely exploded. The update strategy is only applied to records added to databases since April 2019, therefore potentially relevant results published prior to this date are likely to have been missed.
2.4 Were restrictions based on date, publication format, or language appropriate?	No.	The update (June 2020) searches are restricted to records added to databases from April 2019 onwards. Given that the search strategy has been substantially amended since the earlier searches in 2017 and 2019, the EAG believes that the update search should have been applied for the dates up to 2003 to either replace or supplement

		the original search (CS Appendix D.1.1 Search strategy) to ensure that any potentially eligible studies missed by the original search in April 2019 would not have be picked up by the update search. Conference proceedings were sought from 2016 onwards only. A search of older conference proceedings may have identified further trials that were never published, to counter publication bias. There are no restrictions on publication format or language in the search strategies.
2.5 Were efforts made to minimise errors in selection of studies?	Probably Yes.	Record screening was undertaken by two independent reviewers for both title/abstract screening and full text screening for the wider SLR. However, details for the final step of selecting studies to align with the NICE decision problem are not reported.
Concerns regarding methods used to identify and/or select studies	Unclear concern.	While the search included a comprehensive range of databases and additional methods such as grey literature and hand searches, there were notable concerns in the original search strategy and restrictive

		update searches. The original search was less sensitive, contained errors, and did not fully explore relevant terms, while the update searches only included records from April 2019 onwards, potentially missing earlier studies. Additionally, details of supplementary searches and final selection steps were not fully reported, leading to unclear concerns in those areas.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	Yes.	Standardised form used, extraction by one reviewer and verification by a second reviewer.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes.	Characteristics of one study meeting the decision problem were presented in the main report or Appendix. The other included studies were also tabulated.
3.3 Were all relevant study results collected for use in the synthesis?	No	Only one study was selected after conducting the SLR. The relevance of other studies identified in this review is unclear.
3.4 Was risk of bias (or methodological quality) formally	Probably yes.	The methodological quality of the included non-randomised clinical trials (i.e., single-arm trials and observational studies) was

assessed using appropriate criteria?		assessed using the modified Downs and Black checklist. However, this has not been provided by the company. For randomised controlled trials (RCTs), the NICE recommended questions to assess risk of bias were used.
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably yes.	All quality and risk of bias assessment were validated by a second reviewer and conflicts resolved by a third reviewer.
Concerns regarding methods used to collect data and appraise studies	Unclear concern.	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted in line with the scope. However, the CS did not present all of the studies as some were selected out using another set of criteria.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Yes	The company included all the relevant studies
4.2 Were all predefined analyses followed or departures explained?	No information.	There were no pre-defined analyses specified in the CS.

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Not applicable.	The company had only identified one eligible head-to-head comparison RCT to inform the clinical evidence. Therefore, no indirect treatment comparisons were conducted for this submission.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Not applicable	See above
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable, see 4.3.	Not applicable
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	The review makes no reference to the risk of bias in the trial when discussing the results.
Concerns regarding the synthesis and findings	Some concern	The narrative synthesis did not discuss the ROB in the results.
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	Some concern	The review shows some concerns regarding adherence to predefined objectives and eligibility criteria, ambiguity in eligibility criteria, and unclear

		information regarding predefined analyses. However, efforts were made in data collection, study appraisal, and minimising errors in selection and assessment of studies.

7.2 *Appendix 2: Cochrane RoB 2 assessment by EAG*

Table 38: EAG assessment of risk of bias of TRANSFORM trial

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Permuted-blocks method with a dynamic block size, stratified by response to 1L therapy (refractory versus relapse) and sAAIPI (0–1). Interactive response technology.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN	The CS describes the demographic characteristics as 'reasonably well-balanced', however the EAG notes that the SOC arm had a higher proportion of patients aged under 65 years, with ECOG PS 0 at screening (but not at baseline) and who were men. The implications of this are not clear and the imbalances may be to chance.
	Risk of bias judgement	**Low**	
Bias due to[30] deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PY	The FDA[30] statistical reviewer noted that the EFS endpoint, which included starting a new antineoplastic therapy due to efficacy concerns, could be biased in an open-label trial, as investigators could put more SOC participants into a new

			therapy, either intentionally or unintentionally. However, it was noted that a similar number of participants in each arm met this EFS component. The high proportion of crossover from SOC to liso-cel could suggest investigator bias towards liso-cel. Approaches to censor or not censor people who crossed over can also introduce bias. See section 2.2.8 for further comment on the effects of crossover.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY	Where people who crossed over were censored, the remaining sample was unbalanced. Where censoring did not occur, benefit from crossover was included in the analysis. See section 2.2.8 for further comment.
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N	The protocol did not allow crossover from liso-cel arm to SOC
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data available for the primary and key secondary outcomes. Note that only around half of participants formed the HRQoL set (baseline and at least one post-baseline HRQoL), but this was similar between treatment arms (CSR Table 14.1.2.1). Compliance rates varied across the different measures throughout the study
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Objective measures using defined criteria
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Open-label study, but efficacy assessed by an independent review committee.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Unlikely, objective measures using defined criteria, assessed by an independent review committee.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	The study protocol states that details were described in the statistical analysis plan. This was not initially provided to the EAG but was provided in response to Clarification question A19.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

7.3 *Appendix 3 Additional literature searches undertaken by the EAG*

Run 14th and 17th June 2024

Ovid MEDLINE(R) ALL 1946 to June 14, 2024

1 Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3

(lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA] 36200

2 (Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL] 7781

3 1 or 2 41728

4 Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY] 2683265

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf. 1923

6 (3 and 4) or 5 10021

7 Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-

plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE] 29301

8 Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION] 689511

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf. 59064

10 (1 or 9) and 7 and 8 1355

11 6 or 10 [R/R DLBCL OR TRANSFORMED SUBTYPES] 11104

12 randomized controlled trials as topic/ or clinical trials as topic/ or exp randomized controlled trial/ or clinical trial/ or random allocation/ or double blind method/ or single blind method/ or controlled clinical trial/ or cross-over studies/ or placebos/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kf. [RCTs] 2709114

13 11 and 12 2133

14 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or Non-Randomized Controlled Trials as Topic/ or Controlled Before-After Studies/ or Interrupted Time Series Analysis/ or Historically Controlled Study/ or Control Groups/ or trial.ti. or controlled clinical trial.pt. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT?) or (control$ adj3 ("before and after" or "before after")) or time series or (pre-adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kf. [NON-RANDOMIZED STUDIES] 1655388

15 11 and 14 521

16 Observational study/ or exp Cohort Studies/ or Retrospective Studies/ or Case-Control Studies/ or Cross-Sectional Studies/ or Registries/ or Comparative Study/ or (cohort? or (longitudinal or prospective or retrospective or Cross-Sectional) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison or noncomparative or non-comparative) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or "single arm" or "real world" or registr$).tw,kf. [OBSERVATIONAL] 6289459

17 11 and 16 3591

18 13 or 15 or 17 4839

19 exp Animals/ not (exp Animals/ and Humans/) 5231654

20 18 not 19 4808

21 ((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/) 1500901

22 20 not 21 4776

23 (comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt. 2818454

24 22 not 23 4688

25 2024*.dt,ez,da,ed. 870492

26 24 and 25 219

27 limit 24 to yr="2024 -Current" 213

28 26 or 27 225

29 exp systematic reviews as topic/ or exp meta-analysis as topic/ or exp Technology assessment, biomedical/ or (systematic review or meta analysis).pt. or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence

adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kf. [SRs/NMAs/MAs] 608952

30 11 and 29 207

31 30 not 19 207

32 31 not 21 206

33 32 not 23 204

34 limit 33 to yr="2024 -Current" 19

35 25 and 33 19

36 34 or 35 19

Embase Classic+Embase 1947 to 2024 June 14

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56201

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or

((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14818

3 1 or 2 64865

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3830117

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4772

6 (3 and 4) or 5 24577

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46734

8 cell transformation/ or transform$.tw,kw. 781298

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95519

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26317

12 clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or exp randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or triple blind procedure/ or prospective study/ or "randomized controlled trial (topic)"/ or "clinical trial (topic)"/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kw. 4518024

13 11 and 12 8148

14 exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or time series analysis/ or pretest posttest control group design/ or controlled study/ or control group/ or trial.ti. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT$1) or (control$ adj3 ("before and after" or "before after")) or "time series" or (pre- adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kw. [NON-RANDOMISED RCTs] 11637043

15 11 and 14 10369

16 cohort analysis/ or retrospective study/ or longitudinal study/ or prospective study/ or follow up/ or family study/ or observational study/ or population research/ or exp comparative study/ or exp case control study/ or cross-sectional study/ or register/ or (cohort? or (longitudinal or prospective or retrospective) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or (cross-section$ or crosssection$) or "single arm" or "real world" or registr$).tw,kw. [OBSERVATIONAL] 8686403

17 11 and 16 14183

18 13 or 15 or 17 19057

19 (animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp. 2609963

20 (exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/ 8419450

21 18 not (19 or 20) 18564

22 (exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/)) 3066259

23 21 not 22 18271

24 (editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.)) 3118452

25 23 not 24 17972

26 limit 25 to yr="2024 -Current" 502

27 limit 26 to dc=20240101-20240614 494

28 26 or 27 502

29 systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/ or biomedical technology assessment/ or network meta-analysis/ or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kw. [SRs/NMAs/MAs] 906769

30 11 and 29 667

31 30 not (19 or 20) 662

32 31 not 22 655

33 31 not 24 655

34 limit 33 to yr="2024 -Current" 29

35 limit 32 to dc=20240101-20240617 52

36 34 or 35 52

Cochrane Library

Date Run: 17/06/2024 14:59:06

ID Search Hits

#1 MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] this term only 668

#2 ((large or diffuse*) near/2 (b-cell* or bcell* or "cell b") near/3 (lymphoma* or NHL)):ti,ab,kw 2054

#3 ((diffuse* large or large diffuse*) near/3 (lymphoma* or NHL)) or (histiocytic* near/2 (lymphoma* or NHL)):ti,ab,kw 2492

#4 (("T rex lymphoma" or TINHL or tiNHL) or (T-immunoblastic near/1 NHL) or DLBCL):ti,ab,kw 1365

#5 #1 or #2 or #3 or #4 2561

#6 MeSH descriptor: [Lymphoma, Follicular] this term only 453

#7 (3B or IIIB or three-B or "grade 3"):ti,ab,kw 30825

#8 #6 and #7 70

#9 (second* near/2 (central nervous system or CNS) near/2 (lymphoma* or NHL or involvement or relaps*)):ti,ab,kw 20

#10 (SCNSL or SCNS) or (((follicul* near/2 (lymphoma* or NHL)) or FL) near/2 (3B or IIIB or three-B or "grade 3")):ti,ab,kw 235

#11 (FL3B or 3BFL) or (("high grade" or HG or HGL) near/3 (lymphoma* or NHL)):ti,ab,kw 437

#12 (double hit near/1 (lymphoma* or NHL)) or (MYC near/3 (BCL2 or BCL-2 or BCL6 or BCL-6) near/7 (lymphoma* or NHL)):ti,ab,kw 77

#13 ((primary mediastin* or primary media-stin*) near/4 (lymphoma* or NHL)):ti,ab,kw 1222

#14 ((mediastin* or media-stin* or thymic*) near/2 (b-cell* or bcell* or cell b) near/2 (lymphoma* or NHL)):ti,ab,kw 116

#15 (tFL or "transformed follicular lymphoma" or PMBCL):ti,ab,kw201

#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 2028

#17 #5 or #16 4005

#18 MeSH descriptor: [] explode all trees 0

#19 MeSH descriptor: [] explode all trees 0

#20 MeSH descriptor: [] explode all trees 0

#21 MeSH descriptor: [Recurrence] this term only 16370

#22 MeSH descriptor: [Treatment Failure] explode all trees 4166

#23 MeSH descriptor: [Salvage Therapy] this term only 1006

#24 (recurren* or resistan* or refract* or relaps* or "refractory/relapsed" or recrudescen*):TI,AB,KW 228215

#25 (secondline* or second-line*) or (fail* near/2 (treatment or therap*)) or ((fail* or lack) near/2 respon*) or (nonrespon* or non-respon* or unrespon* or unrespon* or no respon* or (not NEXT respon*)):TI,AB,KW 41109

#26 (reappear* or re-appear* or reoccur* or re-occur*) or (salvage near/2 (therap* or treatment* or regime*)):ti,ab,kw 4242

#27 ((refract* or relaps*) near/3 (b-cell* or bcell* or cell b) near/3 (lymphoma* or NHL)):TI,AB,KW 661

#28 #21 OR #22 OR #23 OR #24 OR #25 OR #26 258324

#29 #17 AND #28 1891

#30 #29 OR #27 2115

#31 MeSH descriptor: [] explode all trees 0

#32 MeSH descriptor: [Leukemia, Hairy Cell] this term only 56

#33 MeSH descriptor: [Waldenstrom Macroglobulinemia] this term only 68

#34 (richter* near/2 (transform* or syndrome*)):TI,AB,KW 129

#35 (("marginal zone" or "mucosa-associated" or MALT) near/3 (lymphoma* or NHL)):ti,ab,kw 440

#36 (maltoma or MZL or (primary cutaneous near/3 (lymphoma* or NHL))):ti,ab,kw 328

#37 (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?):ti,ab,kw 2

#38 Hairy cell* or (leuk?emi* near/2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)):ti,ab,kw 165

#39 (histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) near/2 (lymphoma* or NHL)) or (waldenstrom* near/2 (macroglobulin* or macro-globulin* or macroglobin*)) or ((low-grade or slow* or indolent) near/3 (lymphoma* or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL"):ti,ab,kw 1116

#40 MeSH descriptor: [] explode all trees 0

#41 transform*:ti,ab,kw 12796

#42 (((bcell or b-cell or cell b) near/3 lymphoma*) or ((high grade or aggressive or fast*) near/3 (lymphoma* or NHL)) or ((refract* or relaps*) near/3 lymphoma*)):ti,ab,kw 7998

#43 #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 1783

#44 #5 or #42 8089

#45 #41 and #44 397

#46 #44 and #45 397

Limited to published date studies published in 2024

CENTRAL = 3

ASCO 2024 Conference abstracts

DLBCL 15 results

“Diffuse Large B Cell Lymphoma” 26 results

“Follicular Lymphoma” 20 results

“Primary Mediastinal Large B Cell Lymphoma” 0 results

“High Grade Non-Hodgkin's Lymphoma” 0 results

Embase

"European Society for Medical Oncology".nc. limited to 2023-current 0 results

European Hematology Association – 2024 takes place on 13th16th June 2024

American Society of Hematology conference 2024 takes place December 7-10, 2024

American Association for Cancer Research 2024

“DLBCL”, “Diffuse Large B Cell Lymphoma”, “Follicular Lymphoma”, “Primary Mediastinal Large B Cell Lymphoma”, “High Grade Non-Hodgkin's Lymphoma”, “High-grade B-cell Lymphoma” 26 results

European Organisation for Research and Treatment of Cancer 2024 is held on 10-13th June

International Workshop on non-Hodgkin Lymphoma 2024 is held on 19-24 September 2024

International Conference on Malignant Lymphoma 2024 will be held in July 2024

Clinical.Trials.gov

DLBCL", "Diffuse Large B Cell Lymphoma", "Follicular Lymphoma", "Primary Mediastinal Large B Cell Lymphoma", "High Grade Non-Hodgkin's Lymphoma", "High-grade B-cell Lymphoma" 28 results

World Health Organization Clinical Trials Registry WHO ICTRP

"DLBCL OR Diffuse Large B Cell Lymphoma OR Follicular Lymphoma OR Primary Mediastinal Large B Cell Lymphoma OR High Grade Non-Hodgkin's Lymphoma OR High-grade B-cell Lymphoma"

12 results

Trial RecordsEuropean Union Drug Regulating Authorities Clinical Trials Database

"DLBCL", "Diffuse Large B Cell Lymphoma", "Follicular Lymphoma", "Primary Mediastinal Large B Cell Lymphoma", "High Grade Non-Hodgkin's Lymphoma", "High-grade B-cell Lymphoma" 1 result

Economics and utilities, HRQoL and economic models

Carried out 19th June 2024

Ovid MEDLINE(R) ALL 1946 to June 18, 2024

1 Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf.
36229

2 (Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high

grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. 7787

3 1 or 2 41761

4 Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. 2672314

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf. 1929

6 (3 and 4) or 5 10005

7 Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. 29315

8 Cell Transformation, Neoplastic/ or transform$.tw,kf. 689930

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf. 59115

10 (1 or 9) and 7 and 8 1356

11 6 or 10 11091

12 Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or exp models, economic/ or markov chains/ or monte carlo method/ or exp Decision Theory/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or markov or monte carlo or budget$ or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kf. 773149

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 409886

14 (Economics/ or exp "Costs and Cost Analysis"/ or Economics, Dental/ or exp "Economics, Hospital"/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj1 money) or budget$).ti,ab.) not (((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [MEDLINE - NHS EED Econ filter - tested for performance] 1284782

15 (cost$ or cost benefit analys$ or health care costs).mp. [MEDLINE - Economics - McMaster balanced filter] 941195

16 exp "Costs and Cost Analysis"/ or costs.tw. or cost effective$.tw. [MEDLINE - Costs - McMaster balanced filter] 578986

17 12 or 13 or 14 or 15 or 16 1525262

18 "Cost of Illness"/ or "Length of Stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 267641

19 "Facilities and Services Utilization"/ or Utilization Review/ or Concurrent Review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCE UTILIZATION TERMS] 92682

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - MEDLINE] 1771348

21 11 and 20 265

22 exp Animals/ not (exp Animals/ and Humans/) [ANIMAL STUDIES ONLY - REMOVE - MEDLINE] 5233374

23 (address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE] 2923008

24 21 not (22 or 23) [ANIMAL STUDIES and OPINION PUBLICATIONS - REMOVED - MEDLINE] 263

25 2024*.dt,ez,da,ed. 893960

26 24 and 25 28

27 limit 24 to yr="2024 -Current" 28

28 26 or 27 28

29 Quality-Adjusted Life Years/ 16507

30 (quality adjusted or adjusted life year$).ti,ab,kf. 25685

31 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 15743

32 (illness state? or health state?).ti,ab,kf. 8899

33 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2110

34 (multiattribute$ or multi attribute$).ti,ab,kf. 1468

35 (utility adj3 (score? or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 21646

36 utilities.ti,ab,kf. 10018

37 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,kf. 19101

38 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 6551

39 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 27879

40 (time trade off? or time tradeoff? or tto or timetradeoff?).ti,ab,kf. 2513

41 quality of life/ and ((quality of life or qol) adj (score? or measure?)).ti,ab,kf. 16671

42 quality of life/ and ec.fs. 10964

43 quality of life/ and (health adj3 status).ti,ab,kf. 12479

44 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 7895

45 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change? or impact? or impacted or deteriorat$)).ab. 58562

46 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 5604

47 *quality of life/ and (quality of life or qol).ti. 66288

48 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 45401

49 quality of life/ and health-related quality of life.ti,ab,kf. 48085

50 models,economic/ 11197

51 or/29-50 237888

52 (((vignette? or vignette-based or "vignette based") adj3 (stud$ or descript$)) or ("cross-sectional" adj3 (survey? or questionnaire?))).ti,ab,kf. 87146

53 (AQoL or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or ((15D or 15 Dimension) adj2 utilit$) or ("visual analog scale?" or "visual analogue scale?" or VAS or VAS-pain) or FACIT or FACIT-Fatigue or "FACIT Fatigue" or FACIT-F or "Lee Fatigue" or (LFS adj5 utilit$) or VAS-Fatigue or "Piper Fatigue Scale" or PFS or "Schwartz Cancer Fatigue Scale" or SCFS-6 or FACT or FACT-G or "Functional Assessment of Cancer Therapy" or FACT-Lym or "Functional Assessment of Chronic illness Therapy-Lymphoma" or (FACT-G and (Lymphoma Subscale or LymS)) or "EORTC QLQ-C30" or "EORTC-8D" or "NCCN-FACT FLymSI-18" or AML-QOL or QOL-AML).ti,ab,kf. 433234

54 35 and 53 1825

55 51 or 52 or 54 321425

56 11 and 55 82

57 56 not (22 or 23) 82

58 25 and 57 10

59 limit 57 to yr="2024 -Current" 10

60 58 or 59 10

Embase Classic+Embase <1947 to 2024 June 18>

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex

lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56232

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14822

3 1 or 2 64898

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3831987

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4776

6 (3 and 4) or 5 24588

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2

(macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46749

8 cell transformation/ or transform$.tw,kw. 781772

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95585

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26328

12 economics/ or cost/ or exp health economics/ or budget/ or statistical model/ or probability/ or monte carlo method/ or decision theory/ or decision tree/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or budget$ or markov or monte carlo or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kw. 1956427

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 577665

14 12 or 13 2140495

15 (health economics/ or exp economic evaluation/ or exp health care cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [Embase NHS EED Econ filter - tested for performance] 1932857

16 (cost or costs).tw. 1019661

17 14 or 15 or 16 2773753

18 "cost of illness"/ or "length of stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 465780

19 "facilities and services utilization"/ or health care utilization/ or utilization review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCES UTILIZATION TERMS - Embase] 239647

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - Embase] 3201204

21 11 and 20 1675

22 (exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE] 8257561

23 (editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase] 3513802

24 21 not (22 or 23) 1633

25 limit 24 to yr="2024 -Current" 50

26 limit 24 to dc=20240101-20240619 115

27 25 or 26 115

Embase Classic+Embase <1947 to 2024 June 18>

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex

lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56232

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14822

3 1 or 2 64898

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3831987

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4776

6 (3 and 4) or 5 24588

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2

(macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46749

8 cell transformation/ or transform$.tw,kw. 781772

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95585

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26328

12 economics/ or cost/ or exp health economics/ or budget/ or statistical model/ or probability/ or monte carlo method/ or decision theory/ or decision tree/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or budget$ or markov or monte carlo or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kw. 1956427

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 577665

14 12 or 13 2140495

15 (health economics/ or exp economic evaluation/ or exp health care cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [Embase NHS EED Econ filter - tested for performance] 1932857

16 (cost or costs).tw. 1019661

17 14 or 15 or 16 2773753

18 "cost of illness"/ or "length of stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 465780

19 "facilities and services utilization"/ or health care utilization/ or utilization review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCES UTILIZATION TERMS - Embase] 239647

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - Embase] 3201204

21 11 and 20 1675

22 (exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE] 8257561

23 (editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase] 3513802

24 21 not (22 or 23) 1633

25 limit 24 to yr="2024 -Current" 50

26 limit 24 to dc=20240101-20240619 115

27 25 or 26 115

28 Quality-Adjusted Life Years/ 37761

29 (quality adjusted or adjusted life year$).mp. 51199

30 (qaly$ or qald$ or qale$ or qtime$).mp. 29055

31 (illness state? or health state?).mp. 15675

32 (hui or hui1 or hui2 or hui3).mp. 4446

33 (multiattribute$ or multi attribute$).mp. 1718

34 (utility adj3 (score? or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).mp. 39292

35 utilities.mp. 16254

36 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).mp. 38282

37 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).mp. 10000

38 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).mp. 47771

39 (time trade off? or time tradeoff? or tto or timetradeoff?).mp. 3831

40 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).mp. 35439

41 quality of life/ and ec.fs. 66848

42 quality of life/ and (health adj3 status).mp. 38852

43 (quality of life or qol).mp. and Cost-Benefit Analysis/ 7913

44 ((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change? or impact? or impacted or deteriorat$)).tw. 243581

45 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).mp. 1339

46 *quality of life/ and (quality of life or qol).ti. 117544

47 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).mp. 109504

48 quality of life/ and health-related quality of life.mp. 83772

49 models,economic/ 3639

50 or/28-49 535535

51 (((vignette? or vignette-based or "vignette based") adj3 (stud$ or descript$)) or ("cross-sectional" adj3 (survey? or questionnaire?))).mp. 105062

52 (AQoL or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or ((15D or 15 Dimension) adj2 utilit$) or ("visual analog scale?" or "visual analogue scale?" or VAS or VAS-pain) or FACIT or FACIT-Fatigue or "FACIT Fatigue" or FACIT-F or "Lee Fatigue" or (LFS adj5 utilit$) or VAS-Fatigue or "Piper Fatigue Scale" or PFS or "Schwartz Cancer Fatigue Scale" or SCFS-6 or FACT or FACT-G or "Functional Assessment of Cancer Therapy" or FACT-Lym or "Functional Assessment of Chronic illness Therapy-Lymphoma" or (FACT-G and (Lymphoma Subscale or LymS)) or "EORTC QLQ-C30" or "EORTC-8D" or "NCCN-FACT FLymSI-18" or AML-QOL or QOL-AML).mp. 744667

53 50 or 51 or (52 and 34) 634468

54 11 and 53 431

55 limit 54 to dc=20240101-20240619 49

56 limit 54 to yr="2024 -Current" 22

57 55 or 56 49

International HTA database INAHTA

Lisocabtagene maraleucel 0 results

“DLBCL”, “Diffuse Large B Cell Lymphoma”, “Follicular Lymphoma”, “Primary Mediastinal Large B Cell Lymphoma”, “High Grade Non-Hodgkin's Lymphoma”, “High-grade B-cell Lymphoma”

5 results

Total results pre-duplication: 952

Results post duplication: 757

7.4 *Appendix 4 Sources of prices used in EAG confidential appendix (provided separately)*

Name	Form	Dose per unit	Pack size	Price used in this version of appendix
Liso-cel	N/A	N/A	N/A	PAS discount
Axi-cel	N/A	N/A	N/A	PAS discount
Cyclophosphamide	IV	500.0 mg	1 vial	eMIT (updated 5 April 2024)
Dexamethasone (Oral)	Oral	4.0 mg	50 tablets	eMIT (updated 5 April 2024)
Dexamethasone (IV)	IV	3.3 mg	10 ml	eMIT (updated 5 April 2024)
Cytarabine	IV	100.0 mg/ml	5 ml	eMIT (updated 5 April 2024)
Cisplatin	IV	1.0 mg/ml	100 ml	eMIT (updated 5 April 2024)
Fludarabine	IV	50.0 mg	1 vial	eMIT (updated 5 April 2024)
Rituximab	IV	10.0 mg/ml	20 ml	Midpoint MPSC
Gemcitabine	IV	100.0 mg/ml	10 ml	eMIT (updated 5 April 2024)
Carmustine	IV	100.0 mg	1 vial	eMIT (updated 5 April 2024)
Carboplatin	IV	10.0 mg/ml	45 ml	eMIT (updated 5 April 2024)
Etoposide	IV	20.0 mg/ml	5 ml	eMIT (updated 5 April 2024)
Ifosfamide	IV	2000.0 mg	1 vial	MPSC (nationwide price)
Melphalan	IV	50.0 mg	1 vial	eMIT (updated 5 April 2024)
Bendamustine	IV	100.0 mg	1 vial	eMIT (updated 5 April 2024)
Oxaliplatin	IV	5.0 mg	10 ml	eMIT (updated 5 April 2024)
Methylprednisolone	IV	500.0 mg	1	eMIT (updated 5 April 2024)
Chlorambucil	PO	2.0 mg	25	MPSC (nationwide price)
Lomustine	PO	40.0 mg	20	MPSC (nationwide price)

Epirubicin	IV	2.0 mg	5 ml	eMIT (updated 5 April 2024)
Polatuzumab vedotin	IV	30.0 mg	1 vial	PAS discount
Glofitamab	IV	1.0 mg/ml	2.5 ml	PAS discount
Obinutuzumab	IV	25.0 mg/ml	40.0 ml	PAS discount
Loncastuximab Tesirine	IV	10.0 mg	1 vial	PAS discount
Epcoritamab	IV	4.0 mg	1 vial	PAS discount
Tocilizumab	IV	200 mg	1 vial	Midpoint MPSC
Cuvitru	IV	10g/50ml	1 vial	MPSC (nationwide price)

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 12 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect implementation of EAG base case

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
<u>EAG error in subsequent treatment distribution</u> In Section 3.2.8.2 and in scenario EAG07, the EAG prefer to use the subsequent treatment distribution informed by clinical expert opinion, instead of the TRANSFORM trial, and prefer to align to the distributions provided in Table 28 of the report. The EAG have implemented this change incorrectly in the model. When the EAG base case macro is run, cell I42 on "Treatment Distribution" tab is changed to 66.25% as expected, to reflect the proportion of patients expected to receive CAR-T therapy estimated by clinical experts.	<u>EAG error in subsequent treatment distribution</u> Remove the formula from cell E42 on the "Treatment Distribution" tab. The Company would like to highlight the functionality to switch between the TRANSFORM and clinician subsequent treatment distributions has already been implemented in the model in cell E35 and therefore request the new EAG drop downs make use of this functionality. If the EAG wish to retain the functionality to vary the proportion of patients modelled to receive subsequent CAR-T therapy by +/- 15%, this should be implemented in cell I49 of the treatment distribution tab. <u>EAG error in curve choice</u> The results given in the report should be amended to align with the distribution preferences for PFS2 described by the EAG.	<u>EAG error in subsequent treatment distribution</u> The current EAG base case substantially underestimates the proportion of patients receiving subsequent treatment, and therefore, the costs of subsequent treatment, in the SOC arm, as a result of this error. In the TRANSFORM trial, [redacted] patients received at least one subsequent treatment (out of a total of [redacted] TTNT events), meaning that the correct proportion of patients who should receive a subsequent treatment should be [redacted]/[redacted] = [redacted]%. This proportion would then be multiplied by 66.25%, to determine the proportion of patients specifically receiving a 3L CAR-T cell therapy. In fact, as detailed below, this proportion should be 100% in	1) The EAG's implementation of subsequent treatment was as intended, however we accept that the rationale was omitted from our report. This has now been added into section 3.2.8.3. 2) The EAG accepts there was a mistake in implementing the EAG base case around the choice of PFS2 curves. The EAG has updated all analyses using the correct choice of PFS2 curves. 3) The EAG is unclear whether there is an

However, cell E42 is also updated to 66%, which the Company believes to be an error. Cell E42 represents the proportion of patients in the SOC arm receiving **any** subsequent treatment. The EAG have made no comment about changing this input in the report, and there is no clear justification for doing so. The Company believe this change to be an error.

EAG error in curve choice

The model settings required to match the results of EAG01 given in the report do not match those described in section 3.2.6.2.

The EAG base case results, scenario analyses results and results of EAG07 should also all be corrected.

Description of Change	**ICER (£/QALY)**
Original EAG base case	*£38,563*
Correction of subsequent treatment implementation	£230.82
Correction of curve choice implementation	£38,638.41
Cumulative corrected EAG base case	**£231.27**

Additional error identified by the Company

The Company would also like to highlight the original company model contained a slight error in the scenario using clinical the scenario using subsequent treatment distributions from UK clinical experts.

EAG error in curve choice

In section 3.2.6.2, regarding scenario EAG01, the report states that the EAG preference for PFS2 extrapolation distributions are Weibull and log-logistic for liso-cel and SOC, respectively. However, in the EAG base case in the model provided, and to get the reported results, the EAG instead use log-logistic and log-normal. The updated results provided align with the described EAG preferences.

Additional error identified by the Company

For the scenario using the clinical estimates for subsequent treatment distributions (i.e. scenario 13 of the CS), the Company calculated the proportion of patients receiving subsequent error as the company describe. The footnote to the relevant table from the company's advisory board meeting suggests that data from TRANSFORM were provided in a similar way to how they were implemented within the model (a proportion of those who experienced an EFS event), and it is reasonable to assume that the advisors provided this information in the same context.

	expert estimates to inform subsequent treatment distributions. In this scenario, cells E41 and E42 of the model should be 100%. **Description of Change** / **ICER (£/QALY)** Updated results of Company Scenario 13 (probabilistic) / -£2,030.59 (Dominant, ICER in NW quadrant)	therapy in the liso-cel and SOC arms as [redacted]% or [redacted]% * clinician estimate for subsequent treatment market share, respectively. This was based on the proportion of patients receiving subsequent treatment in each arm from TRANSFORM. However, the Company note in the advisory board, clinicians were asked: "Please provide estimates for the proportion of patients with R/R LBCL who are SCT-eligible that might receive each treatment in your clinical practice at some point after receiving liso-cel or SoC at 2L" The wording of the question means the clinical experts were providing an estimate for the market shares of subsequent treatments out of all patients receiving 2L treatment, not those already known to receive a subsequent treatment. As such, it is more appropriate to	

		assume 100% of patients receive subsequent treatment in scenarios using subsequent treatment distributions from UK clinical experts. This does not apply to scenarios which use subsequent treatment distributions from TRANSFORM. The EAG base case and scenario results should be corrected to address the EAG's errors and the Company's additional error, accordingly.	

Issue 2 Discrepancy between modelled efficacy and costs in EAG base case

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
In Section 3.2.8.2 and in scenario EAG07, the EAG prefer to use the subsequent treatment distribution informed by clinical expert opinion, instead of the data from the TRANSFORM trial.	The Company request the EAG update their base case to align the efficacy and costed treatments. • If the EAG prefer to keep EAG05 (bridging therapy) and EAG07 (subsequent treatments) to align with UK clinical practice in their base	The EAG base case approach for modelling PFS-2 and OS uses data from TRANSFORM and ZUMA-7, for both the liso-cel and SOC arms. The use of data from ZUMA-7 is associated with separate concerns (see Issue 4).	Not a factual error.

Page **92** states: "The EAG considers the subsequent treatment distribution of novel therapies to not reflect UK practice. Based on clinical experts consulted from the Company the EAG prefers to alternative chemotherapy regimens for 3L+ chemotherapy as outlined in Table 28". However, while the subsequent treatment costs were updated to reflect UK clinical practice, no attempt was made to adjust the efficacy. Similarly, the EAG base case (and EAG05) prefers to assume 89% of patients receiving CAR-T therapy will require bridging therapy rather than the 63% in the company base case, which was based on the percentage in TRANSFORM.		case, then the modelled efficacy for PFS-2 and OS should be updated to also reflect UK clinical practice. The Company would urge the EAG to consider scenario 13 in the original company submission, which attempted to capture the expected changes in efficacy associated with the changing subsequent treatment distribution in both arms. In this scenario, the Company used a more optimistic curve for liso-cel OS to account for the increased efficacy that would be expected in clinical practice due to the availability of bispecifics. At the same time, the Company also used a weighted average SOC OS curve which comprised of 66.25% of the liso-cel SOC OS extrapolation from TRANSFORM, and 33.75% of the CORAL OS extrapolation. These percentages were based on the assumption that TRANSFORM is representative of patients	However, the EAG then use estimates from clinical experts to inform the subsequent treatment distribution, which the EAG consider more accurately reflect UK clinical practice. This introduces a clear discrepancy between the source of data for subsequent treatment costs, versus the efficacy data, introducing significant bias. In the liso-cel arm, the data from both TRANSFORM and ZUMA-7 is expected to underestimate clinical outcomes compared to UK clinical practice. This is because, in TRANSFORM, only one patient received either epcoritamab or glofitamab and the majority of patients in both trials received 3L+ treatment with chemotherapy regimens. Chemotherapy is associated with significantly worsened outcomes versus novel bispecific therapies, which now represent UK clinical practice.	

Inclusion of EAG05 and EAG07 in the EAG's base case approach leads to a discrepancy between the treatments informing efficacy in the model and the treatments informing costs. This approach is misleading as changing costs without corresponding adjustments to efficacy does not accurately represent real-world scenarios and is inconsistent with UK clinical practice. Therefore, the current EAG base case does not represent an accurate modelling approach that should be considered by the Committee.	receiving 3L+ CAR-T and CORAL is representative of patients not receiving 3L+ CAR-T (to account for potential overestimate of TRANSFORM OS SOC). The Company acknowledge there are limitations with this approach, however, there are no plausible alternatives to allow for adjustment of the liso-cel and SOC OS curve to truly reflect the change in OS outcomes that would likely be associated with changing the subsequent treatment distributions. This suggested approach would at least ensure bridging therapy costs, subsequent treatment costs and efficacy are all modelled to aim to reflect UK clinical practice, for consistency and would increase the QALYs associated with the liso-cel arm. • Alternatively, if the EAG prefer to keep their approach to modelling PFS-2 and OS, then	In UK clinical practice (and the EAG base case), it is estimated 81% of patients would receive 3L+ bispecifics. Therefore, PFS-2 and OS for patients receiving liso-cel would be expected to be substantially improved compared to the TRANSFORM trial. This was supported by UK clinical experts, who unanimously agreed the OS for the liso-cel arm in TRANSFORM is underestimated as patients in the trial primarily received 3L chemotherapy whereas in UK clinical practice they would now receive bispecifics at 3L, which will offer a greater survival benefit.[1] The modelled efficacy for liso-cel should therefore be uplifted compared to data from TRANSFORM and ZUMA-7, to capture the efficacy benefit associated with novel bispecifics. Instead, for PFS-2, the EAG opt to use the Weibull model	

	the base case should be updated to remove EAG05 (bridging therapy) and EAG07 (subsequent treatments). Removing these changes, and reverting to data informed by TRANSFORM, would ensure the modelled efficacy is aligned with the costs included for the bridging therapy and subsequent treatment distributions. This approach would be more broadly aligned with Company clarification B3 and EAG01.	which, as stated on Page 74, has an associated cure rate of [redacted]% and is lower than the 5 year overall survival rate observed in ZUMA-7 ~52%. Similarly for OS, Figure 7 of the EAG report demonstrates the current EAG base case curve for liso-cel OS is underestimated compared to TRANSFORM. The approaches to modelling liso-cel efficacy are therefore inaccurate in scenario EAG07 and the EAG base case as they fail to capture the improved efficacy associated with the costed subsequent treatments. The current approach heavily biases the results against liso-cel, as patients are modelled to receive expensive bispecifics without capturing any efficacy gains associated with these treatments. Thus the EAG's base case approach is not appropriate and does not	

		accurately represent real-world scenarios. At the same time, in the SOC arm, data from TRANSFORM are likely to be overestimated versus UK clinical practice for two reasons. Firstly, all patients were apheresed prior to randomisation, allowing patients to receive 3L+ CAR-T more quickly than they would after SOC in UK clinical practice. Secondly, their T-cells would likely be healthier as they would not have been subjected to 2L reinduction therapy, HDCT and ASCT, and thirdly more patients received 3L+ CAR-T ([redacted]%) compared to what is expected in UK clinical practice (66.25%). For these reasons, in Scenario 13 of the Company CS, the company used a weighted average SOC OS curve which comprised of 66.25% of the liso-cel SOC OS extrapolation from TRANSFORM, and	

		33.75% of the CORAL OS extrapolation. These percentages were based on the assumption that TRANSFORM is representative of patients receiving 3L+ CAR-T and CORAL is representative of patients not receiving 3L+ CAR-T. In UK clinical practice, approximately 66.25% of patients would be expected to receive 3L+ CAR-T cell therapy following liso-cel, and the remaining 33.75% of patients would not. The EAG have made no such adjustment to PFS-2 or OS in the SOC arm, which further biases the results of this scenario against liso-cel as the SOC arm benefits from the efficacy of a higher proportion of patients receiving 3L+ CAR-T therapy without the drawbacks of the increased cost of this treatment.	

Issue 3 Lack of clarity with approach to discounting

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 72, Section 3.2.5 states: "The EAG disagrees with the annual application of a discount rate during the weekly cycle period of the economic model used in the company base case and prefers a per cycle discount rate for this period instead." However, in Table 20, the EAG report notes the approach to discounting is in line with the NICE reference case. It is therefore unclear why the EAG have changed the approach to discounting, when the Company's original approach aligned with the NICE reference case.	The Company request the EAG report is updated to provide additional context to acknowledge the Company's original approach was in line with the NICE reference and clarify why the EAG have changed this.	The Company are unclear why the EAG have made this change as the original approach was in line with the NICE reference case. Furthermore, in prior appraisals such as TA902, the Company's original approach to apply annual application of the discount rate during the weekly cycle period has been accepted, and as part of TA898, it was concluded that both annual and continuous discounting were valid approaches. Furthermore, the Company request the EAG considers a discount rate of 1.5% in the model, in recognition of the transformative nature of liso-cel and the substantial health benefits that it may provide to patients. Per the NICE guidance for health technology evaluations, a non-	The EAG has updated Table 20 to better reflect the EAG perspective. The EAG do not consider the 1.5% discount rate suitable due to the availability of 3rd line CAR T therapy which does not seem to be factored into the company justification.

		reference case discount rate of 1.5% should be considered if: • The technology is for people who would otherwise die or have a very severely impaired life. • It is likely to restore them to full or near-full health. • The benefits are likely to be sustained over a very long period. The Company believe this appraisal meets all three required criteria. <u>The technology is for people who would otherwise die or have a very severely impaired life</u> Outcomes for patients with early relapsed/primary refractory LBCL who are eligible for SCT are poor and only an estimated 10% of patients will be cured with current 2L SOC and approximately half of people with early relapsed/primary refractory LBCL treated with ASCT will experience a further relapse.[2] In a	

		retrospective study of 299 patients with R/R LBCL receiving 2L SOC in the UK between 1st January 2003 to 30th September 2018, 41.8% were eligible for ASCT but did not proceed to ASCT. For this population, the median EFS was 2.6 months and the median OS was 9.4 months.[3] Furthermore, studies reporting outcomes for people with early relapsed/primary refractory LBCL who are eligible for SCT and receiving current SOC, demonstrated patients experience a median EFS of 2.4 months or less, with durable remissions observed in fewer than a quarter of patients (2-year EFS rates for patients treated 2L SOC ranges from [redacted]%).[4-6 7]These results further highlight the poor survival rates in this population. <u>It is likely to restore them to full or near-full health</u> In TRANSFORM, at the time of the final DCO (October 2023), the stratified EFS HR of 0.38 (95% CI: 0.26, 0.54) indicates that liso-	

		cel is associated with a 62% reduction in the risk of experiencing disease progression, death, an inadequate response to treatment or the start of a new antineoplastic therapy versus SOC.[8] Clinical experts estimate that 95% of patients living event-free at two years will achieve long-term remission. Applying this estimation to the two-year EFS rates observed in the TRANSFORM trial suggests that approximately [redacted] of patients will achieve long-term cure following treatment with liso-cel, compared to approximately [redacted] following treatment with SOC. The estimated cure rate observed with liso-cel demonstrates the potential for liso-cel to restore patients to near-full health. <u>The benefits are likely to be sustained over a very long period</u> The treatment's mechanism of action, which involves genetically modifying a patient's own T-cells	

		to target cancer cells, suggests a capacity for long-lasting effects. Unlike traditional therapies that may lose efficacy over time, CAR T-cells provide ongoing surveillance against cancer recurrence.	

Issue 4 Inappropriate comparison to ZUMA-7

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Throughout Sections 3.2.6, the EAG leverage data from ZUMA-7 to inform the estimates for long-term survival extrapolations for liso-cel. For example, on page 75, the report states: "Hence the EAG considers ZUMA-7 a more reliable for source for estimating long-term efficacy." However, this comparison to ZUMA-7 is not appropriate for a number of reasons and does not make appropriate use of	The Company urge the EAG to provide additional context around the ZUMA-7 trial and acknowledge limitations associated with using data from this trial to inform the long-term survival in this appraisal.	The use of ZUMA-7 data in this appraisal to inform long-term efficacy is not appropriate for a number of reasons. Most importantly, the design of the TRANSFORM trial more closely reflects UK clinical practice compared to the ZUMA-7 trial that the EAG are using to inform curve selection. In the TRANSFORM trial, bridging chemotherapy included immunochemotherapy, per UK clinical practice. In contrast, the ZUMA-7 trial only permitted corticosteroids as a bridging chemotherapy.[9] In TA895, clinical experts commented this may	Not a factual error.

the data from TRANSFORM, which is more appropriate to modelling the decision problem.		have made clinicians less likely to enrol patients with fast-progressing disease in the trial and thus introduced uncertainty in applicability of the survival outcomes estimated from ZUMA-7 to UK clinical practice.[6, 10] Clinical experts in TA895 also noted this may have resulted in a reduced incidence of Grade 3 or more CRS and neurotoxicity in ZUMA-7 compared to UK clinical practice.[6] In contrast, during the axi-cel appraisal, clinicians commended the TRANSFORM trial for its greater relevance to UK practice.[6] In fact, on Page 90 of the report, the EAG highlight a study by Boyle *et al.* which reported 11% of CAR T patients received no bridging therapy or steroids in the UK, and thus 89% of patients received bridging therapy in the UK.[11] The EAG did not consider the proportion of patients receiving bridging therapy in TRANSFORM (63%) to be applicable to UK clinical practice. To this extent, the generalisability of long-term survival from ZUMA-7 is extremely uncertain, given only corticosteroids were	

		permitted as a bridging therapy and only 36% of patients received this therapy.[9] This represents a clear contradiction in the EAG's approach and highlights the inappropriateness of using the ZUMA-7 trial data to inform curve selection, especially considering the availability of more generalisable data, that includes in the intervention of interest, from TRANSFORM. Where external validation of the liso-cel OS data from TRANSFORM is needed, input from UK clinical experts is more appropriate than ZUMA-7. Secondly, liso-cel and axi-cel are two different treatments with different manufacturing processes. Specifically, the manufacture of liso-cel involves a dual train approach to manufacturing CD4 and CD8 cells, ensuring a consistent 1:1 ratio in every liso-cel infusion unlike other CAR-T products. While Page 78 of the EAG report highlights studies that have compared liso-cel and axi-cel, these are real world evidence or matching adjusted indirect comparisons and therefore are	

		associated with their own limitations that have not been discussed in the report. Finally, there are a number of important differences between ZUMA-7 and TRANSFORM that could account for the differences in observed efficacy results in the intervention arms that have not been considered in the report[12]: • **Patient population:** TRANSFORM included a broader patient population compared to ZUMA-7. While both trials included a majority of patients with DLBCL, unlike ZUMA-7, TRANSFORM also included patients with PMBL and FL. Furthermore, the eligibility criteria of TRANSFORM was broader, meaning the trial included patients with a wider range of bone marrow function, secondary CNS involvement,	

		and comorbidities compared to the ZUMA-7 trial. • **Bridging therapy:** As discussed above, in the TRANSFORM trial, bridging chemotherapy included immunochemotherapy, per UK clinical practice. In contrast, the ZUMA-7 trial only permitted corticosteroids as a bridging therapy. This restriction in the ZUMA-7 trial also potentially limited enrolment of patients with rapidly progressing disease who might have required more intensive bridging therapy into the trial, further impacting the comparability of results between the two studies. • **Cross-over**: In TRANSFORM, cross-over to liso-cel from the SOC arm was per protocol, whereas in ZUMA-7, any crossover between the groups was not planned. This means, unlike ZUMA-7, in TRANSFORM all patients were apheresed prior to	

		randomisation, allowing patients to receive 3L+ CAR-T more quickly than they would after SOC in UK clinical practice. Secondly, their T-cells would likely be healthier as they would not have been subjected to 2L reinduction therapy, HDCT and ASCT. • **Lymphodepleting regimens:** Both trials used the same dose of fludarabine (30 mg/m²) and the same duration of lymphodepletion (3 days). However, the ZUMA-7 trial used a higher dose of cyclophosphamide than TRANSFORM. This difference in lymphodepleting regimens could potentially impact the efficacy and safety outcomes of the CAR T-cell therapies in each trial. Although the clinical significance of these differences is unknown, it nonetheless would be expected to impact the results from both trials making the direct comparison	

		between TRANSFORM and ZUMA-7 data inappropriate. As discussed further in Issue 5, the Company therefore do not consider it appropriate to use data from ZUMA-7 to generate long-term extrapolations for liso-cel.	

Issue 5 Correction of starting age applied in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The Company have identified two errors related to the discussion of mean ages in the report and also the value for mean age applied in the model. EAG report wording Page 72, Section 3.2.3 states "The EAG considers the starting age of the population ([redacted]) to be	EAG report wording The starting age in the CS of [redacted] was based on the mean starting age in the TRANSFORM trial. However, the committee papers of TA895 indicate that 59 is the median age in ZUMA-7 and the mean age at baseline is 57.2. Therefore, the mean starting age modelled in TA895 is 57.2 and not 59 as the EAG suggests.	EAG report wording Comparison of the mean value for the starting age in the TRANSFORM trial with the median value from ZUMA-7 is not appropriate. The mean starting age in the TRANSFORM ([redacted]) and ZUMA-7 trials (57.2) are extremely similar. The Company therefore encourages the EAG to revise this text. Modelling approach Furthermore, the Company therefore do not consider it appropriate to use the **median** age from ZUMA-7 as the	The EAG has amended the reference to the age used in TA895 as suggested, however the EAG has not changed the starting age used in its preferred modelling as this is supported by NHS England data for current 2L CAR T use.

younger than the expected age of a UK relevant population. Indeed, the starting age of a similar appraisal, TA895 had a starting age of 59, based on the age of the population in ZUMA-7 which also matches the mean age of people who have received 2L axi-cel since it entered the CDF (based on data analysed on 17th July 2024 provided by NHS England)." <u>Modelling approach</u> In EAG09, which informs the EAG base case, the mean starting age in the model is updated from [redacted] to align with the starting age used in TA895 and data from the CDF.	Please can the following text be revised: "**Indeed, the starting age of a similar appraisal, TA895 had a starting age of 57.2, based on the age of the population in ZUMA-7 which also matches** the mean age of people who have received 2L axi-cel since it entered the CDF (based on data analysed on 17th July 2024 provided by NHS England)." <u>Modelling approach</u> Furthermore, the Company request the EAG revise their approach to EAG09 given the inaccurate use of ZUMA-7 trial data in this scenario.	input for the **mean** starting age in the model. In addition, Page 66, Section 2.6 states: "In general, the EAG clinical experts are of the opinion that the baseline characteristics of TRANSFORM are broadly representative of people with R/R LBCL seen in clinical practice in the UK." Therefore, given both the EAG's and the Company's clinical experts agreed the baseline characteristics from TRANSFORM were generalisable to UK clinical practice, the mean starting age in TRANSFORM and ZUMA-7 is similar and the issues with the ZUMA-7 trial highlighted in Issue 4, the Company consider TRANSFORM to be the preferred source for this input. This approach would also prevents mixing and matching the sources for the inputs used in the model and represents a more robust approach.	

The Company do not consider this change accurate.			

Issue 6 Divergence from NICE DSU TSD 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 80, Section 3.2.6.3 states: "The EAG conclude that the large OS benefit modelled for liso-cel by the company to be implausible and inconsistent with currently available information. Instead, the EAG uses SurvInt, a freely available tool which can be used when standard modelling approaches fail to provide a plausible extrapolation"	<u>Justification of implausible OS extrapolations</u> The Company request the EAG update the report to provide context around the limitations associated with their comparisons between the TRANSFORM OS extrapolations and both ZUMA-7 and the TRANSFORM PFS-2 extrapolations. <u>Use of SurvInt</u> The Company request the EAG reconsider their approach to use the SurvInt function to model OS in their analysis.	<u>Justification of implausible OS extrapolations</u> The EAG justify the use of the SurvInt functions as they consider the Company's OS extrapolations to be overly optimistic. However, this conclusion is primarily based on comparisons to OS data from ZUMA-7 and to PFS-2 data from TRANSFORM and does not consider the limitations associated with these comparisons. As discussed in Issue 4, the comparison with data from ZUMA-7 is not appropriate and does not take into account key differences between the two trials designs. Furthermore, the comparison to PFS-2 data from TRANSFORM also fails to acknowledge the limitations associated with the PFS-2 data. The large difference observed between	Not a factual error

		the cure rates predicted by PFS-2 and OS is likely due to the difference in censoring between the two endpoints, as per the company response to B3 of the clarifications questions received. Patients were censored from PFS-2 after 36 months as patients were no longer assessed for disease progression after which points, patients were followed up for OS only. As a result, a single death event which occurred after 36 months brought the PFS-2 KM curves down to 0% and would thereby, cause the resulting extrapolations to be lower. This is in spite of a substantial number of patients being alive, as per the OS KM curves presented in Document B, Section B.2.6.3 of the CS. The censoring of patients from PFS-2 after 36 months is therefore a key limitation associated with the use of the PFS-2 data and beyond this timepoint, PFS2 outcome is unlikely to be highly predictive of OS or have	

		the benefit of observing more events than OS, as the EAG suggests. <u>Use of SurvInt</u> There is no recommendation in NICE TSD 14 for using a 3rd party tool to derive survival extrapolations. This type of analysis is also not aligned to the NICE reference case which explicitly state that synthesis of evidence on health effects should be based on systematic review. Choosing an arbitrary method for altering the extrapolations of directly observed data is likely to introduce bias without systematic consideration of alternate methods. The SurvInt function only uses three inputs: survival at two timepoints and an estimated cure fraction. Unlike the extrapolations generated by the Company following NICE TSD 14 and 21, the EAG's approach ignores the majority of available KM data from TRANSFORM and instead arbitrarily chooses two data points to inform extrapolations. Similarly, the cure fraction for this function is arbitrarily chosen based on PFS-2 data,	

		whereas the mixture cure models used by the Company in line with NICE TSD 14 and 21, leverage the available KM data to calculate a cure fraction. In the extrapolation of liso-cel OS, the EAG choose data from two different studies, TRANSFORM and ZUMA-7, to inform the SurvInt function. As discussed above in Issue 4, there are notable differences in the trial designs between these two studies and therefore it is not appropriate to combine evidence without further consideration of the underlying populations and trial designs. For the SOC extrapolations, it is stated that TRANSFORM extrapolations are not appropriate, however the SurvInt function uses TRANSFORM data to inform its extrapolation. While the Company TRANSFORM extrapolations use all KM data to inform extrapolations, the EAG pick two arbitrary survival points from the TRANSFORM data to inform their extrapolation.	

		Relatedly, the EAG have not provided any justification for why the two timepoints selected in the SurvInt function were chosen, nor have they provided any sensitivity analysis using data from different timepoints. It is therefore unclear how the timepoints were chosen and the impact of the chosen timepoints has on the extrapolations generated by the SurvInt function. In using the SurvInt function, the EAG is therefore excluding evidence from TRANSFORM which is likely to introduce bias in the extrapolations.	

Issue 7 EAG presumption on overestimation of cure proportion due to data immaturity

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 81, Section 3.2.6.3 states "For SOC, the company select a log-normal model based on statistical goodness-of-fit, despite	The Company requests the EAG to revise the text on the overestimation of the cure proportion being attributed to solely the immaturity of the data.	There are other potential reasons which contribute to the overestimation of the cure proportions in the SOC arm which have been explained in detail in the Document B, page 95 of the CS. Firstly, all patients in the TRANSFORM trial, including those randomised to SOC, underwent apheresis prior to commencing treatment at 2L. In	Not a factual error. The EAG has explored the company's collection of estimates from clinical experts, and it suggests that the predictions were specific to the trial arms, rather than real world practice.

acknowledging that all candidate models likely overestimated long-term survival. The cure proportions ranged from 50-55% which were outside the range predicted by their clinical experts ([redacted]). The EAG agrees that due to the immaturity of the data, it is likely that the cure proportion is overestimated by all models."		contrast, in UK clinical practice, patients would undergo apheresis at 3L and only after progression on 2L treatment. In clinical practice, patients cells would therefore be exposed to 2L immunochemotherapy, HDCT and ASCT, before subsequently being apheresed ahead of CAR-T cell therapy. In contrast, in the TRANSFORM trial, because patients were apheresed before randomisation and therefore had only received one line of systemic treatment, the T-cell fitness was likely improved compared to patients who are apheresed in the 3L setting. In addition, earlier apheresis in the trial also resulted in a fast turnaround time of [redacted] between progression on 2L treatment and subsequent receipt of 3L+ CAR-T observed in the TRANSFORM trial. Potentially for these reasons, it should also be noted that the proportion of 3L CAR-T usage in the TRANSFORM was higher than expected in UK clinical practice. These factors would therefore result in a relative overestimation of cure proportions in the SOC arm since patients were able to receive CAR-T therapy without the delay observed in clinical practice which would otherwise have a negative impact of OS. The Company therefore, notes that it is important to consider all these factors in tandem when	Hence the EAG's statement is valid.

		commenting on the overestimation of cure proportions in the SOC arm, rather than solely considering data maturity.	

Issue 8 Inappropriate use of Boyle *et al.* to inform bridging therapy distribution

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 90, Section 3.2.8.1.2 states "Clinical experts consulted by the EAG suggested that the proportion of patients receiving bridging therapies and the distribution of bridging therapies will differ from those currently modelled in the company base case. In a study of CAR T use in the UK, Boyle *et al*. reported that 11% of CAR T patients received no bridging therapy or steroids.[11] The EAG also prefers	The Company would like to highlight that the bridging distribution in Boyle *et al.* may not be reflective of the UK clinical practice for reasons stated in the "Justification for amendment" column and therefore requests the EAG to acknowledge the limitations in the selection of Boyle *et al.* to inform the bridging therapy distributions.	As noted in Document B, Section 3.5.1, page 162, the Company acknowledged that UK clinical expert feedback indicated that most patients would receive R-GDP, R-ICE or Pola-BR, in addition to radiotherapy and corticosteroids. However, the clinical experts further highlighted that the recent recommendation for Pola+R-CHP in 1L (March 2023) was likely to result in the substantial reduction of Pola-BR use in 2L in the near future.[1, 13] A high proportion of patients (64.04%) assumed by the EAG to receive Pola-BR based on Boyle *et al.* which had a study period of 2018 to 2019 and 2020 to 2022, and therefore, would not take into account the effect of the recent recommendation for Pola+R-CHP in 1L.[11] Furthermore, the	Not a factual error.

to use the distribution of bridging therapies taken from Boyle *et al.*[11] Table 27 compares the preferred assumptions relating to bridging therapy by the company and EAG.”		Boyle *et al.* study included patients who received CAR-T therapy in the 3L setting and therefore does not reflect the bridging therapy usage in the 2L setting. The number of patients receiving bridging therapy at 2L as well as the bridging therapy distribution would likely be different to the 3L setting as, at 3L, patients would have already been exposed to the majority of bridging therapy treatments at 2L (as SOC re-induction chemotherapy) and would not be re-exposed at 3L. The EAG bridging assumption is therefore unlikely to be reflective of UK clinical practice as it does not consider the changing landscape of the use of bridging therapies and the differences between 2L and 3L.	

Issue 9 Inaccurate risk of bias assessment for TRANSFORM

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 65, Section 2.2.4 states: “The EAG judged TRANSFORM to have a	The Company request the EAG update the report to provide important additional context here.	The Company acknowledge that open label trials which allow per-protocol crossover could result in the confounding of study	Not a factual error, this is the view of the EAG. In addition, the EAG provide justification for their assessments of the

high risk of bias overall because of the risk of bias due to deviations from the intended interventions inherent in the design of TRANSFORM." However, this misrepresents the appropriateness of the TRANSFORM trial design and does not include the appropriate context.		outcomes. However, in this instance, including crossover from the experimental arm to the control arm as part of the study protocol has been viewed as a strength of the TRANSFORM study and was a criticism of the ZUMA-7 trial, as crossover is deemed patient centric and aligned to real-world clinical practice.[6] Furthermore, the proportion of patients who crossed over from the control arm to the experimental arm in TRANSFORM was comparable to that in ZUMA-7, despite crossover not being part of the ZUMA-7 protocol, 66.3% and 56% respectively. This illustrates how aligned the TRANSFORM study design is to UK clinical practice and that the high proportion of crossover is unlikely to be a result of investigator bias. Finally, in their statistical review of the Company's BLA 125714/90 submission which was based on the TRANSFORM data, the FDA concluded that since the observed number of subjects who met the EFS component was very similar between the control and	ROB2 signalling questions of "Were there deviations from the intended intervention that arose because of the experimental context?" and "Were these deviations likely to have affected the outcome?" in Table 38 in Appendix 2.

		experiment arms, it was not necessary to conduct further analysis on the primary efficacy endpoint. For these reasons, the company believe that it is important to clarify the benefits of study trial design to prevent misrepresenting the TRANSFORM trial.	

Typographical Errors

Issue 10 Typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12, Section 1.7, Table 2, Row 4: "EFS 02: Discount applied per cycle"	Please can this be amended as follows: **EAG02:** Discount applied per cycle. The remaining rows of the table should then be renumbered accordingly to align to the numbering of exploratory	Typographical error. We believe that this row was incorrectly labelled when comparing to the exploratory analyses on Page 97 and Table 33 on Page 98, Section 5.1.1.	This has been amended.

	analyses on Page 97, Section 5.1.1.		
Page 17, Section 1.2.1 states “Large B-cell lymphomas (LBCL) are one of 12 families of mature B-cell neoplasms. The CS accurately cites HMRN data, estimating that 5,440 people are newly diagnosed with LBCLs each year in the UK, with an annual incidence of 8.3 cases per 100,000 people.”	Please can this be amended as follows: Large B-cell lymphomas (LBCL) are one of 12 families of mature B-cell neoplasms. The CS accurately cites HMRN data, estimating that 5,440 people are newly diagnosed with LBCLs each year in the UK, with an annual incidence of **3.8** cases per 100,000 people.	Typographical error. The correct incidence value reported in the cited paper (Tilly *et al.* 2015) is 3.8 cases per 100,000 people. The company would like to acknowledge that this value is also listed incorrectly in Document B, page 19 and page 21 of the CS, and apologises for this oversight.	The total cases of 5440 relates to an incidence of 8.3 per 100,000, see https://hmrn.org/statistics/incidence (LBCLs under ‘mature B-cell neoplasms’) as reported by HMRN. As Tilly was a secondary reference the EAG did not report data reported in Tilly but only the HMRN
Page 17, Section 1.2.1 states “In the UK, DLBCL is the most common type of LBCL, accounting for 40% of all NHL cases (approximately 4,870 cases, typically presenting in older adults and characterised by aggressive, heterogeneous clinical features.”	Please can this be amended as follows: In the UK, DLBCL is the most common type of LBCL, accounting for 40% of all NHL cases (approximately **4,780** cases, typically presenting in older adults and characterised by aggressive, heterogeneous clinical features).	Typographical error. We assume the calculation used with the cited data as the number of DLBCL cases being 40% of 11,940 NHL cases (i.e. 4,776). Typographical error. Parenthesis missing.	4,870 is from the HMRN statistics (reference 5 in the EAG report), https://hmrn.org/statistics/incidence (under diffuse large B-cell lymphoma under Large B-cell lymphomas). We have added the parenthesis.

Page 44, Section 2.2.7 states “As noted elsewhere (see section **Error! Reference source not found.**), a high proportion ([redacted]) of the SOC arm crossed over to liso-cel, though [redacted].”	Please can this be amended as follows: “As noted elsewhere (see section **Error! Reference source not found.**), a high proportion ([redacted]) of the SOC arm crossed over to liso-cel, though [redacted].”	Data error. The original statement is technically correct, however we would request that this statement be updated to accurately reflect the treatment received.	This has been amended for clarity.
Page 45, Section 2.2.7, Table 8.	Please can the final two rows be amended as follows: Other CAR T: Liso-cel [redacted], SOC [redacted] Total Number of Subsequent Systemic Therapies Received (excluding CAR T, radiotherapy and SCT): Liso-cel [redacted], SOC [redacted]	Data error. From the source table ‘TRANSFORM Analysis Table 1 Summary of Subsequent Anti-cancer Therapies ITT Analysis Set Oct 2023 DCO’, the other CAR-T therapies listed for liso-cel arm are: axicabtagene ciloleucel n=[redacted], CAR-T CELLS NOS n=1, tisagenlecleucel n=[redacted].	This has been amended.
Page 50, Section 2.2.8.2.3 states “Despite this definition, the EAG	Please can this statement be removed.	This is an incorrect interpretation of the PFS-2 data in TRANSFORM and	Not a factual error, as EAG uncertainty is confirmed by company’s statement.

remains uncertain over the analyses performed by the company relating to this outcome, as the information provided by the company suggests people in TRANSFORM could have multiple PFS2 events.”		the label “PFS-2 event status” in some of our tables may have been misleading. Under the original definition of PFS-2 in TRANSFORM, PFS-2 was considering not 1st and 2nd PFS-2 events, but 1st and 2nd PFS events which participate overall in PFS-2. The 1st event is normally the PFS event, while the PFS-2 event in the new (conventional) approach is normally either the 2nd PFS event in the original (recurrent) approach when it existed or still the 1st event at the same date when this one was definitive (death or censor for the first event.	
Page 51, Section 2.2.8.4 states “The company used three questionnaires to capture quality of life information within the TRANSFORM study:	Please can this be amended as follows: The company used three questionnaires to capture quality of life information within the	Typographical error. C is missing from EORTC.	Whilst the page reference is incorrect, this has been amended.

EORT QLQ-C30, FACT-Lym and EQ-5D-5L, see CS Section B.2.6.4.”	TRANSFORM study: EORT**C** QLQ-C30, FACT-Lym and EQ-5D-5L, see CS Section B.2.6.4.		
Page 62, Section 2.5.3, Table 16.	Please can the table be completed.	Data error. Table 16 is incomplete as it is missing the last 5 rows from the source (FDA. *Lisocabtagene maraleucel (Breyanzi)* Silver Spring (MD): U.S. Food and Drug Administration; 2022.Table 61, Page 114–115).	This has been amended.
Page 66, Section 2.6 states “Finally, the subsequent therapies received in TRANSFORM are not reflective of recently approved therapies or UK practice (discussed further in Section 3.2.8.3), including the likelihood of liso-cel arm receiving a second CAR T treatment, and proportions receiving CAR T following SOC.”	Please can this be amended as follows: Finally, the subsequent therapies received in TRANSFORM are not reflective of recently approved therapies or UK practice (discussed further in Section 3.2.8.3), including the ~~**likelihood of liso-cel arm receiving a second CAR T treatment, and**~~ proportions receiving CAR T following SOC.	Typographical error. Retreatment with CAR-T in the liso-cel arm was not permitted in TRANSFORM.	As indicated by the company in their correction earlier in this table relating to Page 45 of the EAG report, additional CAR T was received. Not a factual error.

Page 66, Section 2.6 states “A high proportion ([redacted]) of participants in the SOC arm were eligible to crossover to liso-cel due.”	Please can this sentence be completed or removed.	Typographical error. This sentence appears to be a typo as it is incomplete and currently appears to not be relevant to the paragraph it sits in.	The EAG has amended this sentence.
Page 67, Section 3.1.1 states “Searches for cost-effectiveness and health-related quality of life (HrQoL) evidence were carried out separately in June 2020 on an appropriate selection of bibliographic databases, conference websites and grey literature sources, including websites of relevant HTA organisations.”	Please can this be amended as follows: Searches for cost-effectiveness and health-related quality of life (HrQoL) evidence were carried out separately in **April** 2020 on an appropriate selection of bibliographic databases, conference websites and grey literature sources, including websites of relevant HTA organisations	Typographical error. The correct data are reported in Document B, page 98 and 155 of the CS.	This has been amended.
Page 67, Section 3.1.1 states “A supplementary search was carried out with the inclusion of additional economic terms with no date limit (CS	Please can this be amended as follows: A supplementary search was carried out with the inclusion of additional economic terms with	Typographical error. Incorrect table was referenced.	This has been amended.

Appendix G 1.1. Table 28).”	no date limit (CS Appendix G 1.1. **Table 37**)		
Page 67, Section 3.1.1 states “The searches include database-specific indexing and free-text terms for the population/ condition (R/R DLBCL) combined with filters for costing, economic and HRQoL studies (CS Appendix G.1.1.1 Search strategy Tables 27-36 and Tables 48-56).”	Please can this be amended as follows: The searches include database-specific indexing and free-text terms for the population/ condition (R/R DLBCL) combined with filters for costing, economic and HRQoL studies (CS Appendix G.1.1.1 Search strategy **Tables 26**-36 and Tables 48-56).	Typographical error. Incomplete references to relevant tables were used.	This has been amended.
Page 67, Section 3.1.1 states “The reasonably sensitive and non-validated search filters developed by CADTH (Canadian Agency for Drugs and Technologies in Health),[39] the validated NHS EED Economic filter[40] and the validated balanced McMaster filter[41] for economic and costing	Please can this be amended as follows: The reasonably sensitive and non-validated search filters developed by CADTH (Canadian Agency for Drugs and Technologies in Health),[39] the validated NHS EED Economic filter[40] and the validated balanced McMaster filter[41] for economic and costing studies were applied (CS Appendix	Typographical error. Incomplete references to relevant tables were used.	This has been amended.

studies were applied (CS Appendix G.1.1.1 Electronic database searches Tables 27 and 28)."	G.1.1.1 Electronic database searches **Tables 27-36**).		
Page 68, Section 3.2.1 states "Utility values were derived from the TRANSFORM trial and ZUMA-1 3L axi-cel trial, TA895."	Please can this be amended as follows: Utility values were derived from the TRANSFORM trial for the company base case and ZUMA-1 3L axi-cel trial, TA895 **for relevant scenario analyses**	Clarification on the use of utility values. Utility values from ZUMA-1 3L axi-cel trial, TA895 were only used in relevant scenario analyses.	This has been amended.
Page 69, Section 3.2.2 states "EFS is the primary end point of the trial, defined as failure to achieve CR or PR by 9 weeks or the start of new antineoplastic therapy due to efficacy concerns or death."	Please can this be amended as follows: EFS is the primary endpoint of the trial, defined as **the time from randomisation to progressive disease**, failure to achieve CR or PR by 9 weeks **post-randomisation**, or start of a new antineoplastic therapy due to efficacy concerns or death **from any cause, whichever occurs first**	Typographical error. Definition is reported in Document B, page 59 of the CS.	This has been amended.

Page 70, Section 3.2.2 states “The company prefers the lognormal model for both liso-cel and SOC EFS extrapolation with a predicted EFS cure fraction of [redacted] in the liso-cel arm and [redacted] in the SOC arm.”	Please can this be amended as follows: The company prefers the lognormal model for both liso-cel and SOC EFS extrapolation with a predicted EFS cure fraction of [redacted] in the liso-cel arm and [redacted] in the SOC arm	Typographical error. [redacted] corresponds to the cure fraction estimated by the Weibull model. The correct data are presented in Document B, page 123 of the CS.	This has been amended.
Page 70, Section 3.2.2 states “Parametric models were chosen based on considerations of statistical fit using AIC and BIC criteria, plausibility of long-term extrapolations for combined cured and non-cured fractions, predicted cure fractions and plausibility of extrapolation for non-cured patients and plausibility of hazard functions.”	Please can this be amended as follows: Parametric models were chosen based on considerations of **visual inspection of fit**, statistical fit using AIC and BIC criteria, plausibility of long-term extrapolations for combined cured and non-cured fractions, predicted cure fractions and plausibility of extrapolation for non-cured patients and plausibility of hazard functions.	Typographical error. Considerations for curve selection are detailed in Document B, page 129-130 of the CS.	This has been amended.
Page 70, Section 3.2.2 states “TTNT was defined as the time from randomisation to death or	Please can this be amended as follows: TTNT was defined as the time from randomisation to death **due**	Typographical error. Definition is reported in page 43 of the company	This has been amended.

the start of new antineoplastic therapy.”	**to any cause** or start of new antineoplastic therapy, **whichever occurred first**.	clarification question response to B7.	
Page 72, Section 3.2.4 states “Patients in the intervention group were split into those who received liso-cel infusion (97.8%) and those who did not receive liso-cel infusion ([redacted]%). Infused patients were modelled to incur the full cost of liso-cel and non-infused patients were modelled to incur the cost of leukapheresis and bridging chemotherapy.”	Please can this be amended as follows: “Patients in the intervention group were split into those who received liso-cel infusion (97.8%) and those who did not receive liso-cel infusion ([redacted]%). Infused patients were modelled to incur the full cost of liso-cel and non-infused patients were modelled to incur the cost of leukapheresis and bridging chemotherapy. **Of the 90 infused patients, one patient received a non-conforming product infusion. Costs associated with CAR-T acquisition for patients who received a non-conforming product were not accounted for, although administration costs were included in line with patients receiving liso-cel**.”	Clarification on the cost incurred by patients who received a non-conforming product infusion. The corresponding clarification is reported in Document B, page 107 of the CS.	This has been amended.

Page 72, Section 3.2.4 states "Patients in the comparator group were modelled to receive SOC which included re-induction immunochemotherapy followed by HDCT (98.9%) and ASCT (46.7%)."	Please can this be amended as follows: "Patients in the comparator group were modelled to receive SOC which included **re-induction immunochemotherapy (98.9%) followed by HDCT** ~~(98.9%)~~ **and ASCT (46.7%)**."	Typographical error. 98.9% refers to the proportion of patients receiving re-induction immunochemotherapy whilst 46.7% refers to the proportion of patients receiving HDCT and ASCT.	This has been amended.
Page 76, Section 3.2.6.3 states "The company report in their text that the most plausible range of the cure proportion predicted by their experts was [redacted], however Table 40 of the company submission suggests that this range is in fact [redacted]."	Please can this be amended as follows: "The company report in their text that the most plausible range **of the most likely values** for the cure proportion predicted by their experts was [redacted].~~however Table 40 of the company submission suggests that this range is in fact [redacted].~~"	Typographical error. The range of [redacted] to [redacted] corresponds to the range of the most likely values for cure proportions predicted by clinical experts consulted, as per Document B, Table 40, page 134. The range [redacted] to [redacted] corresponds to the average clinician estimate of the lower plausible limit and higher plausible limit for cure proportions.	This has been amended.
Page 77, Section 3.2.6.3 states	Please can this be amended as follows:	Inappropriate word choice. The use of "gentler profile" is not a scientific	This has been amended.

"The EAG notes that across outcomes, that liso-cel shows short term benefit compared to axi-cel, however the benefit appears to reduce as follow-up increases. This could be attributed to the gentler profile of liso-cel compared to axi-cel, and the EAG do not consider the evidence strong enough to support a long-term benefit."	"The EAG notes that across outcomes, that liso-cel shows short term benefit compared to axi-cel, however the benefit appears to reduce as follow-up increases. ~~This could be attributed to the~~ **Liso-cel has a more favourable safety profile** ~~of liso-cel~~ compared to axi-cel, and the EAG do not consider the evidence strong enough to support a long-term benefit."	description. The CS has described liso-cel to have a "more favourable safety profile" throughout multiple instances of Document B. The company would also like to highlight that attributing the difference in efficacy to the more favourable safety profile of liso-cel is an overly simplistic presumption.	
Page 84, Section 3.2.6.4 states "A TTNT event included death or starting a subsequent treatment. Hence, after estimating the TTNT curve, the company then apply a multiplier, scaling down the incidences of beginning new treatment, based on the proportion of new-treatment events out of all TTNT events."	Please can this be amended as follows: "A TTNT event included death or starting a subsequent treatment. Hence, after estimating the TTNT curve, the company then apply a multiplier, ~~scaling down the incidences of beginning new treatment~~, based on the proportion of ~~new-~~**subsequent** treatment events out of all TTNT events, **to calculate the total proportion of patients who**	Inappropriate word choice. The use of "scaling down" suggests that the proportion of subsequent treatment events have been reduced via this calculation. The correct data are reported in Document B, Section B.3.5.2, page 169 of the CS.	Not a factual error.

	received at least one subsequent treatment.		
Page 87, Section 3.2.7 presents Table 25 Summary of health-state utility values used in the base case economic analysis and PFS-2 scenario analysis	Please can the table be amended to clearly delineate which values correspond to the base case economic analysis and PFS-2 scenario analysis.	N/A	This has been amended.
Page 88, Section 3.2.8 states “Patients who received non-conforming product were assumed to incur only CAR T tariff costs.”	Please can this be amended as follows: “~~Patients who received non-conforming product were assumed to incur only CAR T tariff costs~~. **For patients who received non-conforming product, patients were assumed to incur CAR T tariff and administration costs. Costs associated with CAR-T drug acquisition were not accounted for**.”	Typographical error. The correct data are reported in Document B, Section 3.5.1, page 161 of the CS. As administration costs are not included in the CAR-T tariff, the proposed amendment is a more accurate reflection of the costs incurred by patients receiving non-conforming products.	This has been amended.
Page 92, Section 3.2.8.3 states “For 3L+ chemotherapy, patients were assumed to receive	Please can this be amended as follows: “For 3L+ chemotherapy, patients were assumed to receive 100%	Typographical error. The correct data are reported in Document B, Section	This has been amended.

100% R-Bendamustine. Only drug acquisition costs were considered at 3L+. Drug administration costs and AE costs were not considered.”	R-Bendamustine, **delivered 100% in the outpatient setting**. ~~Only d~~**Drug** acquisition **and administration** costs were considered at 3L+. ~~Drug administration costs and~~ AE costs were not considered.”	B.3.5.2, page 170 of the CS.	
Page 92, Section 3.2.8.3 states “The EAG considers the subsequent treatment distribution of novel therapies to not reflect UK practice. Based on clinical experts consulted from the company the EAG prefers to alternative chemotherapy regimens for 3L+ chemotherapy as outlined in Table 28.”	Please can this text be revised as the EAG’s opinion on the subsequent treatment distribution of novel therapies is not clear. Please can the table be revised and split as necessary as the novel therapy breakdown is not clear and can more information (i.e., time period, patient population, etc.) on the derivation of the NHS England liso-cel and SOC estimates be provided.	Unclear presentation of data.	This has been amended.

Company clarifications

EAG Response: The following are not factual errors.

Location	Description	Company response
Page 21, Section 1.2.2 states “The CS reports the proportions estimated to receive each of these to be 37.5% (range 25-40%), the EAG believes this is a typographical error as CS reference 45 reports rates of 32.5% (which is also used in the health economic model, see CS Table 78).”	N/A	The company acknowledges that the data presented in Document B, page 31 of the CS were incorrect, and should report rates of 32.5% for both glofitamab and epcoritamab as correctly noted by the EAG.
Page 39, Section 2.2.4 states that “In addition, it appears that the company confused concealment of treatment allocation with blinding of assigned interventions during the trial.”	N/A	The Company acknowledge that there was a mistake in Table 13 of the CS in response to the question ““Were the care providers, participants and outcome assessors blind to treatment allocation?” The Company confirm that only participants were blinded to treatment allocation.

Page 48, Section 2.2.8.2.1 states "It is unclear how many people had responses from subsequent therapies that were classed as responders"	N/A	The Company notes responses for those with unknown or missing response who went onto to a subsequent therapy for any reason - either efficacy concerns or other, were not included in the analysis, as stipulated in section 10.6 of the Statistical Analysis Plan. It is stated that 'Subjects with unknown or missing response will be counted as non-evaluable in the analysis. Any responses after a start of a new antineoplastic therapy are not considered'.
Page 73, Section 3.2.6.1 states "The model does not apply background mortality to EFS meaning the EFS extrapolations eventually cross the OS extrapolations."	Please can this be amended as follows: "**All projected EFS curves are capped by the OS curves (which are capped by background mortality) to ensure that the proportion of patients in the EFS health state remains equal to or less than the proportion in the OS health state at any given time over the model time horizon**."	The company would like to clarify that the projected EFS curves were capped by the OS curves, as reported in Document B, page 151 of the CS.
Page 74, Section 3.2.6.2 states "As with EFS, the company model does not apply background mortality of PFS2, meaning it will	Please can this be amended as follows: "**All projected PFS-2 curves are capped by the OS curves (which are capped by background mortality) to ensure that the proportion of**	The company would like to clarify that the same approach was taken for PFS-2 as EFS wherein the projected

converge with the OS extrapolation at some point."	**patients in the PFS-2 health state remains equal to or less than the proportion in the OS health state at any given time over the model time horizon**."	PFS-2 curves were capped by the OS curves.
Page 78, Section 3.2.6.3 states "The EAG identified a real-world study which compared outcomes for people who received liso-cel or axi-cel.[15] This abstract by Portuguese et al. did not show any clear OS benefit for liso-cel (Figure 5). In addition, two published indirect comparisons comparing 3L axi-cel and liso-cel found that axi-cel was associated with a significant OS benefit (HR = 0.53, 95% CI = 0.34-0.82; HR = 0.54, 95% CI = 0.37, 0.79).[16, 17]"	N/A	The Company agrees that two published indirect comparisons found that 3L axi-cel was associated with a significant OS benefit. However, as noted in Document B, Section B.1.3.5, page 34 of the CS, a matching-adjusted indirect comparison by Abramson *et al.* 2022 between 2L liso-cel and axi-cel informed by the TRANSFORM and ZUMA-7 trial data, reported no differences in efficacy outcomes, with a median EFS of 10.1 months (95 CI: 6.1, NR) for liso-cel and 8.3 months (95% CI: 4.5, 5.8) for axi-cel, with a HR of 0.94 (95% CI: 0.58, 1.52).[18] While the company has iterated that it is not appropriate to compare the TRANSFORM trial with ZUMA-7 as explained in Issue 4, the company suggests for the EAG to revise the text on the comparisons made between liso-cel and axi-cel to include the findings from the MAIC

		analyses between 2L liso-cel and axi-cel outlined above.

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