NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatment (review of TA987) [ID6619]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatment (review of TA987) [ID6619]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Bristol-Myers Squibb Pharmaceuticals Ltd:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **NICE medicines optimisation team (MOT) report**

4. **Patient group, professional group, and NHS organisation submission** from:
   a. Anthony Nolan
   b. Lymphoma Action
   c. Clatterbridge Cancer Centre and The Royal College of Pathologists

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

6. **External Assessment Group response to factual accuracy check of EAR**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments [ID6619]

Document B

Company evidence submission

28th November 2025 (Updated 20th January 2026)

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Abbreviations

Abbreviation	Definition
ABC	Activated B-Cell subtype
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ASCT	Autologous Stem Cell Transplant
BLA	Biologics License Application
BMS	Bristol Myers Squibb
BNF	British National Formulary
BOR	Best Overall Response
BSC	Best Supportive Care
CCM	Cost-Comparison Model
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide–Doxorubicin–Vincristine–Prednisone
CHP	Cyclophosphamide–Doxorubicin–Prednisone
CNS	Central Nervous System
CRP	C-Reactive Protein
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data Cut-Off
DL1D	Dose Level 1 (double dose)
DL1S	Dose Level 1 (single dose)
DL2S	Dose Level 2 (single dose)
DL3S	Dose Level 3 (single dose)
DLBCL	Diffuse Large B-Cell Lymphoma
DoR	Duration of Response
DSA	Deterministic Sensitivity Analysis
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group Performance Status
EFS	Event-Free Survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EPAR	European Public Assessment Report
ESS	Effective Sample Size
FDA	Food and Drug Administration
FL3B	Follicular Lymphoma Grade 3B
FLBCL	Follicular Large B-Cell Lymphoma
GCB	Germinal Center B-Cell subtype
GCP	Good Clinical Practice

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Abbreviation	Definition
GDP	Gemcitabine–Dexamethasone–Cisplatin
GFR	Glomerular Filtration Rate
GHS	Global Health Status
GemOX	Gemcitabine–Oxaliplatin
HCRU	Healthcare Resource Use
HDCT	High-Dose Chemotherapy
HGBCL	High-Grade B-Cell Lymphoma
HGLCL	High-Grade Large Cell Lymphoma
HIV	Human Immunodeficiency Virus
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HSCT	Hematopoietic Stem Cell Transplant
HSUV	Health State Utility Value
ICANS	Immune Effector Cell–Associated Neurotoxicity Syndrome
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
INV	Investigator
IPI	International Prognostic Index
IQR	Interquartile Range
IRC	Independent Review Committee
ITT	Intention-to-Treat
IWG	International Working Group
LBLC	Large B-Cell Lymphoma
LDC	Low-Dose Cyclophosphamide
LDH	Lactate Dehydrogenase
LFTU	Long-Term Follow-Up
LoS	Length of Stay
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MAIC	Matching-Adjusted Indirect Comparison
MCL	Mantle Cell Lymphoma
MHRA	Medicines and Healthcare products Regulatory Agency
MoA	Mechanism of Action
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHB	Net Health Benefit
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NOS	Not Otherwise Specified
OECD	Organisation for Economic Co-operation and Development
ORR	Overall Response Rate

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Abbreviation	Definition
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PET	Positron Emission Tomography
PMSI	Programme de Médicalisation des Systèmes d'Information
PMBCL	Primary Mediastinal B-Cell Lymphoma
PRO	Patient-Reported Outcome
PSS	Personal Social Services
QLQ	Quality of Life Questionnaire (EORTC)
RWD	Real-World Data
RWE	Real-World Evidence
SACT	Systemic Anti-Cancer Therapy dataset
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SLE	Systemic Lupus Erythematosus
SMD	Standardised Mean Difference
SOC	Standard of Care
SPD	Study Protocol Deviation
STA	Single Technology Appraisal
TEAE	Treatment-Emergent Adverse Event
TSD	Technical Support Document
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VAT	Value-Added Tax
WHO	World Health Organization
WTP	Willingness to Pay

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

B.1.1 Decision problem

Lisocabtagene maraleucel (liso-cel) received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) in October 2023 for treatment of adult patients with relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy (3L+).[1] In coming to its decision, the MHRA relied on a European Commission decision on 4th April 2022, in accordance with the advice from the European Medicines Agency (EMA) and its Committee for Medicinal Products for Human Use (CHMP).[2]

Liso-cel has receiving marketing authorisation for three additional indications (see Section B.1.2, Table 2):[3]

- Adult patients with DLBCL, high-grade B-cell lymphoma (HGBCL), PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line immunochemotherapy (second-line [2L] positioning)
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (3L+ positioning)
- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (3L+ positioning; EMA only)[4]

The relevant population for this submission is narrower than the marketing authorisation for liso-cel in this indication and comprises adult patients with R/R DLBCL and PMBCL (excluding FL3B) who did not respond to, or relapsed after, two or more lines of systemic therapy. For simplicity, R/R DLBCL and PMBCL will be referred to as R/R LBCL hereafter. Given not all patients within this population are suitable for chimeric antigen receptor (CAR) T-cell therapy, this submission focuses on a targeted population, of those suitable to receive CAR T-cell therapy at 3L+. This includes patients who:

- Relapsed <12 months after first-line (1L) treatment but did not receive autologous stem cell transplant (ASCT) due to ineligibility, then relapsed/progressed post 2L immunochemotherapy and are CAR T suitable at 3L+.
- Relapsed ≥12 months post 1L treatment and were eligible for 2L ASCT but did not respond to reinduction treatment and are CAR T suitable at 3L+.
- Relapsed following 2L ASCT but are suitable to receive CAR T-cell therapy.

In UK clinical practice, treatment choice at 3L+ is guided by a number of factors, including a patient's previous treatment history, and whether they are suitable and willing to receive intensive therapies, such as CAR T-cell therapies.[5] For patients who have not yet received CAR T-cell therapy, and are considered suitable to do so, CAR T-cell therapy is anticipated to represent the main treatment option at 3L+ in UK clinical practice (Section B.1.3.3). In CAR T suitable patients with R/R DLBCL and PMBCL at 3L+, axicabtagene ciloleucel (axi-cel) represents the current standard of care (SoC). Axi-cel received a positive recommendation from the National Institute for Health and Care Excellence (NICE; TA872) for adult patients with DLBCL or PMBCL after two or more systemic therapies and was identified as the main comparator in the NICE final scope for this submission.[6, 7] If recommended, liso-cel is anticipated to represent an alternative to axi-cel as a suitable 3L+ treatment for CAR T suitable patients with R/R DLBCL and PMBCL, providing clinicians with a choice of available CAR T-cell therapies to suit a range of patients. If a technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. BMS therefore

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proposes that liso-cel be assessed against axi-cel under the NICE cost comparison appraisal process, as it believes all the criteria outlined in the NICE manual for health technology evaluations are met:

- Both liso-cel and axi-cel are autologous CD19 directed CAR T-cell therapies with similar mechanisms of action.[8-10]
- The results of a matching-adjusted treatment comparison (MAIC) between liso-cel and axi-cel (see Section B.3.9) demonstrate that the two treatments offer comparable efficacy in the targeted population - patients suitable for CAR T-cell therapy at 3L+. This is supported by UK CAR T Experts consulted as part of this submission who unanimously agreed that the evidence, so far, have been consistent in showing that liso-cel and axi-cel have comparable efficacy at 3L+.[11] The MAIC also showed that liso-cel is associated with [redacted] of adverse events of special interest (AESIs), indicating a superior safety profile compared with axi-cel. Large US real-world evidence (RWE) studies further support the comparable efficacy and favourable safety profile of liso-cel compared with axi-cel .[12-14] UK Clinical Experts confirmed that the baseline characteristics of patients in these studies were generally consistent with those observed in UK practice. Liso-cel is therefore anticipated to provide an improved health benefit given its favourable safety profile compared with axi-cel.
- Axi-cel is the established SoC in UK clinical practice in the targeted population and is prescribed to the vast majority of patients with R/R LBCL who are suitable for CAR T-cell therapy at 3L+ (Section B.1.3.4).[15] Axi-cel was also identified as the main comparator to liso-cel in UK clinical practice in the NICE final scope for this submission (Table 1).[7]
- [redacted]

The decision problem addressed within this submission is outlined in Table 1.

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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	Adults with relapsed or refractory DLBCL or PMBCL, after two or more lines of systemic therapy	Adult patients with R/R DLBCL or PMBCL after two or more systemic therapies who are suitable to receive CAR T-cell therapy	The target population for liso-cel in this submission is narrower than the NICE final scope as it focuses on a targeted population of those suitable to receive CAR T at 3L+. The target population is however in line with the patient population in which axi-cel (the main comparator) is routinely prescribed in clinical practice.[6] This positioning represents a subpopulation of the licensed indication for liso-cel, which excludes patients with R/R FL3B.[1]
Intervention	Lisocabtagene maraleucel	Lisocabtagene maraleucel	In line with NICE final scope
Comparator(s)	**The main relevant comparator is:** • Axicabtagene ciloleucel **Other comparators are:** • Salvage chemotherapy combination regimens with or without rituximab, including: ○ DHAP (dexamethasone, cytarabine, cisplatin) ○ ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ○ GDP (gemcitabine, dexamethasone, cisplatin) ○ GemOX (gemcitabine and oxaliplatin)	Axicabtagene ciloleucel	The target population for liso-cel is adult patients with R/R DLBCL or PMBCL after two or more systemic therapies who are suitable to receive CAR T-cell therapy. Axi-cel represents the most relevant comparator to liso-cel in UK clinical practice for the following reasons: • Both liso-cel and axi-cel are autologous CD19 directed CAR T-cell therapies with similar mechanisms of action • Axi-cel is the established SoC in UK clinical practice in the targeted population and is prescribed to the vast majority of patients with R/R DLBCL and PMBCL at 3L+ who are suitable for CAR T-cell therapy • Liso-cel and axi-cel offer comparable

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	○ ICE (ifosfamide, carboplatin, etoposide) ○ IVE (ifosfamide, epirubicin and etoposide) • Polatuzumab vedotin with rituximab and bendamustine (only when stem cell transplantation is not suitable) • Loncastuximab tesirine (if previously had polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) • Glofitamab • Epcoritamab (if previously had polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) • Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory DLBCL		efficacy in the target population. This is supported by a MAIC (see Section B.3.9), RWE studies and UK CAR T Experts' feedback. Additionally, patients who are suitable for CAR T-cell therapy would likely only receive treatment with CAR T-cell therapy, rather than an alternative therapy. Therefore, the only relevant comparator to liso-cel in the CAR T suitable population at 3L+ is axi-cel.
Outcomes	• Progression-free survival (PFS) • Overall survival (OS) • Response rates, including time to next treatment and duration of response (DoR) • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	All outcomes specified in the NICE final scope are included in the submission as follows: • Response to treatment, including: ○ Overall response rate (ORR; percentage of patients achieving an objective response of partial response [PR] or better) ○ Complete response (CR) rate (percentage of patients achieving a complete response)	In line with NICE final scope

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		○ DoR (time from first documentation of CR or PR to disease progression or death) • OS (time from randomisation to time of death due to any cause) • PFS (time from randomisation to progression, or death from any cause, whichever occurs first) • AEs of treatment • HRQoL using EORTC QLQ-C30 and EuroQol EQ-5D-5L	
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 • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. • 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	• The cost comparison of liso-cel versus axi-cel has been evaluated, in line with the NICE reference case • Costs were considered from a PSS perspective • A patient access scheme (PAS) for liso-cel was included in the analysis	Liso-cel is considered to meet all the criteria for a cost-comparison appraisal, enabling the economic assessment to be conducted through a cost-comparison analysis.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	NHS and Personal and Social Services (PSS) perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups	If evidence allows, the following subgroups will be considered: • Type of lymphoma (DLBCL, PMBCL) • Grade of lymphoma • Number of previous treatments • Previous stem cell transplant	Subgroups from the pivotal TRANSCEND trial were explored and are presented in Section B.3.7.	Subgroups were explored based on available data.

Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CAR: chimeric antigen receptor; CR: complete response; DHAP: dexamethasone, cytarabine and cisplatin; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: EuroQol five dimensions 5-level; ESHAP: etoposide, methylprednisolone, cytarabine and cisplatin; FL3B: follicular lymphoma grade 3B; GDP: gemcitabine, dexamethasone and cisplatin; GemOX: gemcitabine and oxaliplatin; HRQoL: health-related quality of life; ICE: ifosfamine, carboplatin and etoposide; IVE: ifosfamine, epirubicin and etoposide; lis-cel: lisocabtagene maraleucel; MAIC: matching-adjusted indirect comparison; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: overall response rate; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PMBCL: primary mediastinal large B-cell lymphoma; PR: partial response; PSS: Personal and Social Services; QLQ-C30: quality of life questionnaire core-30; R/R: relapse/refractory; SoC: standard of care; TA: technology appraisal; UK: United Kingdom.

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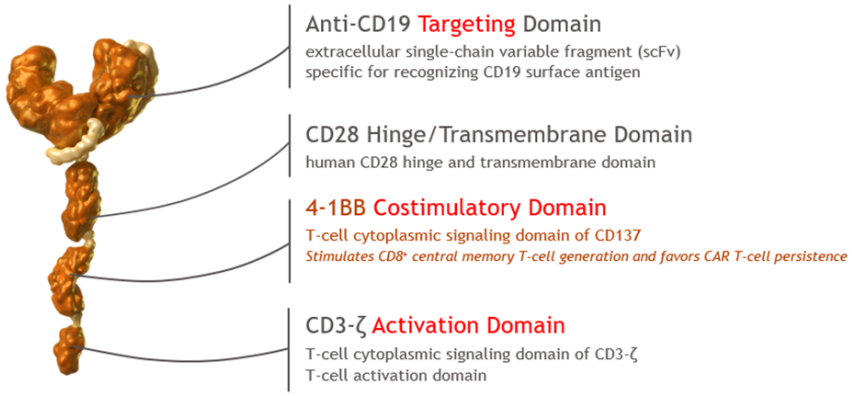
B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with liso-cel for the treatment of patients with R/R LBCL at 3L+ is presented in Table 2.

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

Table 2: Technology being evaluated

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 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.[10] **Figure 1: Structure of liso-cel**  **Abbreviations:** CAR: chimeric antigen receptor; scFv: single chain variable fragment. **Sources:** Makita et al. (2019)[16]; Teoh et al. (2019)[17]; Jayaraman et al. (2020)[18]; Weinkove et al. (2019).[19] **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

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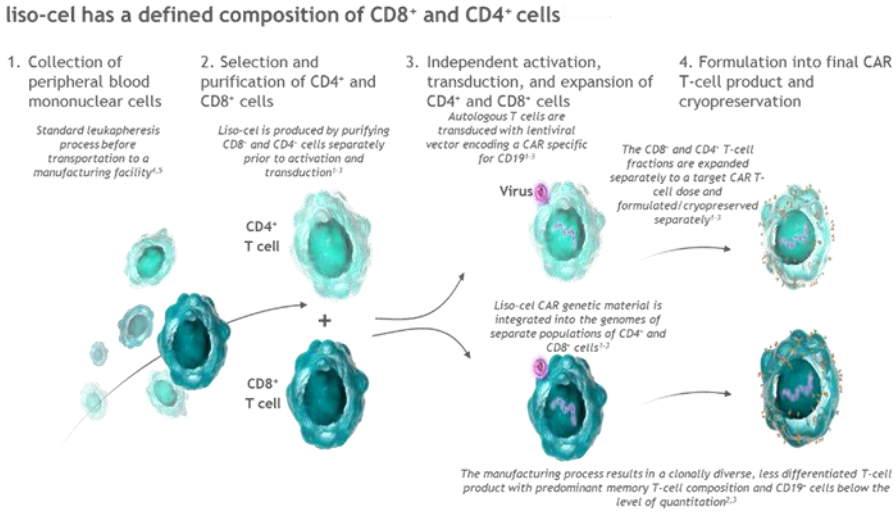
to ensure a fixed number of CAR+ T-cells. Liso-cel is then administered as two separate infusions of CD8+ and CD4+ CAR T-cells at a target 1:1 ratio (Figure 2).[16, 20]

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.[21, 22] 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.[23]

The manufacturing process and defined composition of liso-cel:[20, 24]

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

Figure 2: Liso-cel manufacturing process



Abbreviations: CAR: chimeric antigen receptor.
Sources: Ramsborg et al. (2017)[20];Teoh et al. (2019)[17]; Abramson et al. (2020)[25]; Hucks et al. (2019)[26] and Levine et al. (2016).[27]

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.[28, 29] Expression of CD19 is largely restricted to B lineage cells and is expressed in the majority of B-cell malignancies, including B-cell lymphomas.[30] Liso-cel is therefore able to target malignant cells whilst sparing non-cancerous cells from cytotoxicity, consequently limiting systemic effects.[31]

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.[10] 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.[32] Ligation of the CAR T receptor also leads to CAR T-cell proliferation.[32]

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Marketing authorisation/CE mark status	In October 2023, liso-cel received marketing authorisation from the MHRA for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy..[33] In April 2022, liso-cel received marketing authorisation in the same indication from the EMA.[2]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Liso-cel has received marketing authorisation from the EMA and MHRA for the treatment of: • adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy (EMA: April 2022; MHRA: October 2023) • adult patients with DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line immunochemotherapy (EMA: April 2023; MHRA: September 2024) • adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (EMA: March 2025; MHRA: August 2025) • Adult patients with relapsed or refractory MCL after at least two lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (3L+ positioning; EMA only: November 2025)[4] Contraindications to liso-cel include hypersensitivity to any of the excipients listed in Section 6.1 of the EMA and MHRA SmPCs. Contraindications of the lymphodepleting chemotherapy must also be considered.[1, 2]
Method of administration and dosage	Liso-cel is given as two separate infusions of CD8+ and CD4+ CAR T-cells and is intended for autologous and intravenous use only.[1] A one-off IV infusion of liso-cel contains a target of 100 x 10^6 CAR+ viable T-cells (consisting of a 1:1 ratio of CD8 and CD4 components), suspended in one or more vials of each component. 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). **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

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	and management of CRS and serious neurological adverse reactions, among others.[1] **Monitoring and management after infusion** Patients should be monitored 2–3 times during the first week following infusion, for signs and symptoms of CRS, neurologic events and other toxicities. Physicians should consider hospitalisation at the first signs or symptoms of CRS and/or neurologic events. Frequency of monitoring after the first week should be carried out at the physician's discretion and should be continued for a least 4 weeks after infusion. Patients should be instructed to remain within proximity of the qualified treatment centre for at least four 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 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/commercial arrangement (if applicable)	A confidential Patient Access Scheme (PAS) discount of [redacted]% to the liso-cel list price is available in UK practice, yielding 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.

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

Summary of the health condition

- LBCLs are an aggressive class of non-Hodgkin lymphoma (NHL) characterised by rapidly growing, abnormal B lymphocytes.[34, 35] Around 4,400 patients are newly diagnosed with LBCL each year in the UK, corresponding to an annual incidence of 9.4 cases per 100,000 people (based on diagnoses between 2010 and 2019)[36, 37]
- Numerous subtypes of LBCL exist.[38] DLBCL and PMBCL are the subtypes considered within this submission, aligned with the reimbursed population for axi-cel
- DLBCL is the most common type of NHL, accounting for around 40% of NHL cases.[39] PMBCL is much less common than DLBCL, accounting for around 2–3% of global NHL cases[40, 41]
- Data on LBCL as a whole and the rarer types of LBCL, including PMBCL, are limited. As such, the following sections primarily focus on data for DLBCL, which is considered generalisable to PMBCL given that the disease characteristics and treatment response. For simplicity and brevity, DLBCL and PMBCL will be referred to as LBCL hereafter[42]

Burden of disease

- Compared with the general population, the 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.[43, 44] As patients progress through treatment lines, their HRQoL continues to deteriorate further[45]
- The emotional burden associated with a diagnosis of LBCL is exacerbated for patients with R/R LBCL at 3L+ who are heavily pretreated.[46] As patients move through subsequent lines of therapy, or receive treatment options with generally poor prognosis, they often experience a decline in the hope that they will enter remission, which can contribute to increased emotional strain[47]

UK treatment pathway for LBCL

- LBCL is a curable disease, and approximately 60–70% of patients will be cured after receiving 1L therapy.[48, 49] However, a substantial proportion of patients will not be cured, either because their disease does not respond to treatment (primary refractory LBCL), or because they experience disease relapse following completion of 1L treatment.[49] 1L treatment for LBCL generally involves rituximab-containing immunochemotherapy regimens with curative intent. According to UK CAR T Experts, most patients receive Pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisolone) in this setting[50]
- Patients with LBCL who relapse <12 months after initial treatment and are fit enough the receive ASCT typically receive treatment with liso-cel and axi-cel CAR T-cell therapy at 2L. The introduction of CAR T-cell therapies at 2L in UK clinical practice has significantly improved outcomes for patients with R/R LBCL
- Patients with R/R LBCL who relapse >12 months after initial treatment cannot receive CAR T-cell therapy and instead receive salvage therapies at 2L consolidated with high-dose chemotherapy (HDCT) and ASCT
- Clinical outcomes for patients who relapse <12 months are much worse than those for patient who relapse <12 months after 1L treatment with lower response rates (46% and 88%, respectively) and worse three-year event-free survival (20% and 45%, respectively) [51-53] For patients with R/R DLBCL who are not considered eligible for ASCT glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) was recently recommended by NICE (ID6202)[54]
- Historically, outcomes are particularly poor among patients with R/R DLBCL and PMBCL at third-line and beyond (3L+), the patient population of relevance to this submission. At this stage, patients progress rapidly and palliative care is often the only feasible treatment option[6]
- At 3L+, treatments for patients with R/R LBCL may include glofitamab, loncastuximab tesirine, epcoritamab, chemotherapy or CAR T-cell therapy[50, 55]
- The introduction of the CAR T-cell therapy axi-cel at 3L+ represented a step-change in treatment options for patients with R/R LBCL.[6] Treatment with axi-cel is associated with longer

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OS than immunochemotherapy and sustained PFS, demonstrating notable clinical benefit when compared to the previous SoC in UK clinical practice.[6] Despite the improved efficacy of axi-cel, its tolerability profile is poor, with some patients requiring intensive care unit (ICU) admission for AE management, which contributes to an increased treatment burden for patients and cost burden to the National Health Services (NHS)[56]

- Axi-cel requires inpatient administration which is associated with a significant HRQoL burden, with patients reporting feelings of loneliness and isolation[57]
- Patients who are unsuitable for CAR T-cell therapy, or have previously received CAR T-cell therapy at 2L, typically receive treatment with bispecific antibodies (BsAb)[58]

Liso-cel

- The TRANSCEND trial (the pivotal trial for liso-cel, detailed in Section B.3.3) demonstrated the meaningful overall response rate (ORR), duration of response (DOR), OS and PFS of liso-cel in pretreated R/R 3L+ DLBCL, PMBCL and FL3B patients[59]
- In a MAIC versus axi-cel, a CAR T-cell therapy currently available on the NHS for treating DLBCL and PMBCL after 2 or more systemic therapies, liso-cel has been shown to be associated with a similar efficacy and an improved safety profile[6]
- The introduction of liso-cel to the treatment pathway would provide an alternative CAR T-cell therapy option for patients with R/R LBCL with comparable efficacy but with an improved safety profile. This would enable clinicians to select the best available CAR T-cell therapy for a given patient, considering their individual circumstances, comorbidities, contraindications, and preferences
- The improved safety profile of liso-cel allows it to be delivered in the outpatient setting. This, in addition to the anticipated lower ICU usage, is expected to result in reduced costs relating to the management of AEs with liso-cel treatment compared with axi-cel at 3L+[60]

B.1.3.1 Health condition

Disease overview

NHL comprises a heterogenous group of cancers that begin in the white blood cells, specifically the lymphocytes.[34, 35] LBCLs 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 predominantly accumulating in lymph nodes.[61, 62] 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.[34]

The category of LBCL comprises 12 families/classes of lymphomas that are further classified into types and subtypes; however, as noted previously, within this submission LBCL will refer to DLBCL and PMBCL only. I[63] LBCLs are classified according to the World Health Organisation (WHO) guidelines for lymphoid neoplasms, with their most recent updates occurring in 2016 and 2022.[38, 61, 64, 65] A summary of the classification and epidemiology of the DLBCL and PMBCL subtypes are provided in Table 3. Given the limited data available on the rarer PMBCL subtype, and the generalisability of DLBCL disease characteristics to this other subtype, the evidence described in the following sections primarily focus on data for DLBCL.

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 7.5 cases per 100,000 individuals (diagnoses between 2010 and 2019)[36, 39, 66] • DLBCL is an aggressive disease, with heterogeneity in clinical, pathological and molecular presentation; resulting in varying prognoses[67] • DLBCL is generally composed of large neoplastic (abnormally growing) B lymphoid cells that express CD19, CD20, CD22, CD79a antigens and tends to

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Type	Description of LBCL type
	present in older adult patients, with peak incidence in patients aged 65–74 years[49, 68] • In most cases, the causes of DLBCL are unknown[69]
PMBCL	• PMBCL accounts for 2–3% of NHL cases and 10% of LBCLs.[40] The estimated incidence in the UK is 0.2 cases per 100,000 individuals[39] • PMBCL also expresses CD30, CD23, PDL1 and PDL2 in addition to CD19/20, giving PMBCL a distinct phenotype compared with DLBCL[49] • PMBCL typically develops within the mediastinal area (the area separating the lungs) and mainly affects young adults (25–40 years) and women.[70, 71] Patients therefore often present with cough, tachypnoea, vein thrombosis, chest pain and dysphagia[72, 73] • 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[71]

Abbreviations: CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; NHL: non-Hodgkin lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; UK: United Kingdom.

Risk factors

DLBCL is the result of both genetic and environmental factors.[74] 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]).[49, 75-78] Key modifiable risk factors in DLBCL 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).[75, 77, 79-81]

Prognostic factors for DLBCL

Several prognostic factors for DLBCL 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.[82] The International Prognostic Index (IPI), revised IPI (R-IPI), National Comprehensive Cancer Network-IPI (NCCN-IPI), age-adjusted IPI and secondary aaIPI 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.[49, 72, 83, 84]

This submission focuses on patients with R/R DLBCL 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). A systematic literature review (SLR) of studies in patients with R/R DLBCL at 3L+, published between 2016 and 2021, found that primary refractory disease was identified as a key prognostic factor for clinical outcomes in, by an SLR and clinical expert review.[85] Additional prognostic factors identified included older age, higher IPI composite score, elevated LDH and higher ECOG performance scores.[85] Treatment outcomes for patients with progressive disease after two lines of systemic therapy are poor and get progressively worse with each subsequent line of therapy.[51] The focus of this submission is on patients who have experienced disease progression following 2L treatment, which is indicative of a very poor prognosis. Patients with R/R DLBCL often have reduced response and survival rates at later treatment lines compared with earlier treatment lines.[51]

B.1.3.2 Burden of disease

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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).[35]

As the disease progresses, it spreads to multiple groups of lymph nodes and extranodal sites,[86] and therapies that were previously used to treat the cancer may be used as a means of controlling symptoms only. Organs containing tumours may eventually fail to function properly, which can lead to problems such as difficulty breathing or swallowing, diminished mental capacity, infections, pain and fatigue.[87]

QoL impact

Limited data are available on the HRQoL burden for patients with R/R LBCL. However, a single study collected real-world HRQoL data on 441 patients with DLBCL across Europe and the US.[45] When comparing HRQoL across lines of therapy, a statistically significant reduction in quality of life (QoL) was reported between patients receiving treatment at 1L versus 3L+, with mean EQ-5D-5L utility scores reduced from 0.73 to 0.66, respectively.[45] This highlights the symptom burden and impairment in HRQoL experienced by patients with LBCL, particularly in the 3L+ setting.

Axi-cel, the current SoC for patients with R/R LBCL who are suitable for CAR T at 3L+, requires inpatient administration. Treatments requiring inpatient care can have a greater impact on patient HRQoL compared with those received in an outpatient setting, as patients are less active, are exposed to hospital acquired infections, are able to see their families less frequently and have less freedom in what they eat. In a CAR T patient and caregiver UK report by Stenson *et al.* (2023), patients described disruption to their lives and a loss of normality associated with receiving CAR T as an inpatient. They emphasised the negative impact of intensive monitoring in an inpatient setting and the physical constraints in the hospital, and reported feelings of loneliness and isolation in both a physical and emotional capacity.[57] One patient even described feeling like a “caged animal”, when citing the prolonged hospital admission and monitoring required.[57] This study highlights the need for treatment options for R/R LBCL that offer improved tolerability; can be delivered in an outpatient setting; reduce hospital admissions; and mitigate the physical and emotional burden for patients.

CAR T-cell therapy is associated with toxicities that can require intensive management requiring admission to ICU. The high toxicity profile associated with axi-cel treatment, particularly the high rates of neurologic events (ICANS) and CRS, results in a significant proportion of patients requiring ICU admission in real-world settings. This is supported by French real-world data (RWD) from 2024 that reported [redacted]% and [redacted]% of patients receiving axi-cel at 2L and 3L, respectively, were admitted to ICU.[88, 89] This study also demonstrated how the improved safety profile of liso-cel is reflected in ICU admissions, with only [redacted]% of patients being admitted to ICU following 2L liso-cel treatment. Similarly, a US RWD study reported that, among patients with R/R LBCL having been infused with either liso-cel or axi-cel, a numerically lower proportion of those receiving liso-cel required hospitalisation (liso-cel: 21.2%; axi-cel: 39.6%) or ICU admission (liso-cel: 1.5%; axi-cel 10.4%).[14] Of those who did require hospitalisation, the median length of stay was lower for patients receiving liso-cel compared with axi-cel (9.0 days versus 10.0 days, respectively).

ICU admission for the treatment of CAR T associated toxicities was cited by UK CAR T Experts consulted for NICE TA1048 as the most difficult part of treating patients with CAR T-cell therapies. Prolonged ICU stay often results in muscle wasting, compounded by the effects of high-dose steroids, intubation, and mechanical ventilation. This necessitates extensive physiotherapy and occupational therapy support. Additionally, many patients may be malnourished and require nutritional intervention,

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such as naso-gastric or parenteral feeding, under the guidance of a dietitian. Patients may experience 'post-ICU syndrome', showing signs of depression which requires support from psychologists, and the neurological effects can remain for some time. As discussed in the response to draft guidance in NICE TA1048, UK CAR T Experts noted that, following an ICU stay for the treatment of ICANS and the use of high-dose steroids to treat neurotoxicity, patients will require 2–3 weeks of inpatient rehabilitation to recover from the extreme effects on their neurological and physical condition.[60]

Finally, the impact of an ICU stay on caregivers of patients can be extremely distressing, with clinicians noting that family members also experience a version of post-ICU syndrome called post-ICU syndrome-family, demonstrating the expanded value of reduced ICU admissions with liso-cel.

Economic burden

A retrospective single-centre observational study on 84 patients in Germany detailed the economic burden at different treatment lines, encompassing treatment costs and hospital admissions. This study demonstrated the increasing cost of treatment as patients progress beyond 3L to 4L+ (3L: €32,589; >3L: €88,668), highlighting the need for efficacious treatment options at 3L that prevent further disease progression and the need for later lines of treatment.[90]

As part of NICE TA1048, UK CAR T Experts noted that the favourable safety profile of liso-cel compared with axi-cel, particularly the reduced proportion of patients experiencing high-grade toxicity, would translate to lower ICU usage associated with liso-cel. The strain on ICU following treatment for R/R LBCL is of particular importance. One analysis has shown that the UK had the 2nd lowest bed capacity (after Sweden) in 2021 compared with countries in the EU, as per the Organisation for Economic Co-operation and Development (OECD) database, despite increases in the number of beds.[91] This strain on ICU bed capacity in the UK is further exacerbated by a high adult critical care occupancy rate in England of 79.1%, as recorded by NHS England in October 2024.[91] The availability of more ICU beds would allow for better management of patient flow for other critically ill patients such as patients from Accident & Emergency (A&E), surgery and other hospital wards. This would enable more timely admissions, improving their outcomes by reducing the severity of their conditions upon ICU entry. It was noted in NICE TA1048 that reducing ICU admission for patients receiving CAR T would reduce some of the burden on healthcare providers and services, highlighting the potential cost saving to the NHS should liso-cel be recommended at 3L+.[60]

B.1.3.3 Current UK treatment pathway

The clinical guidelines for LBCL informing UK clinical practice are from the British Society of Haematology (2024), European Society for Medical Oncology (2025), the National Comprehensive Cancer Network (NCCN) 2025 B-cell Lymphomas guideline and NICE recommendations.[6, 55, 58, 92-95] NICE guidelines on the treatment of NHL were developed prior to the availability of CAR T-cell therapies and, therefore, do not provide recommendations on their use.[96] Despite being recognised as distinct disease types, DLBCL and PMBCL are both aggressive forms of LBCL and clinical treatment guidelines from the NCCN recommend they be managed using the same clinical pathway.[72] This is generally the case in UK clinical practice, although some treatment options are only reimbursed for specific LBCL subtypes.[97]

The typical UK treatment pathway for LBCL is presented in Figure 3 and summarised below, based on recent clinical guidelines and published NICE evaluations.[36, 55, 72] This includes the proposed positioning of liso-cel at 3L+.

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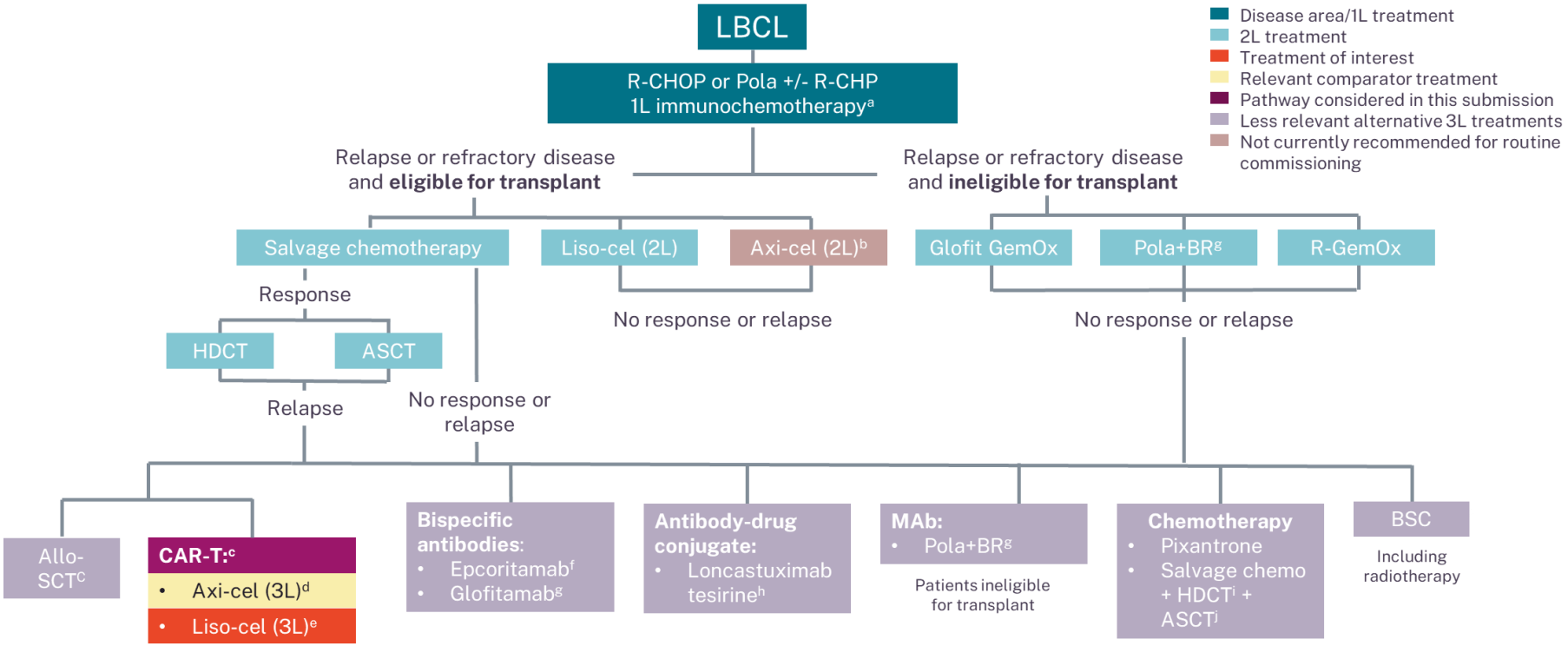
Figure 3: UK treatment pathway for LBCL and the anticipated positioning of liso-cel



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 via the CDF (TA895). [c] CAR T-cell therapies and Allo-SCT are not an option at 3L if CAR T-cell therapies are given at 2L. [d] Axi-cel at 3L is recommended only in patients with DLBCL and PMBCL (TA872). [e] The proposed positing for liso-cel in this submission is in patients with R/R DLBCL and PMBCL at 3L+. [f] Epcoritamab is recommended only in patients with DLBCL (NICE TA954). [g] Glofitamab and Pola+BR at are recommended only in patients with DLBCL (TA927 and TA649). [h] 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). [i] HDCT consists of carmustine/BCNU®, etoposide, cytarabine and melphalan [BEAM]). [j] Salvage chemotherapy + HDCT + ASCT is not available at 3L if it has been received at 2L.
Abbreviations: 1L: first-line; 2L: second-line; ASCT: haematopoietic stem cell therapy; Axi-cel: axicabtagene ciloleucel; BSC: best supportive care; CAR T: chimeric antigen receptor T-cell; CDF: Cancer Drug Fund; DLBCL: diffuse large B-Cell lymphoma; FL3B: follicular lymphoma grade 3B; Glofit GemOx: glofitamab, gemcitabine and oxaliplatin; HDCT: high-dose chemotherapy; liso-cell: lisocabtagene maraleucel; LBCL: large B-cell lymphoma; MAb: monoclonal antibody; PMBCL: primary mediastinal B-cell lymphoma; Pola+BR: polatuzumab vedotin, bendamustine, rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-GemOx: rituxiab, gemcitabine and oxaliplatin.
Source: NICE TA895;[97] NICE TA954; NICE TA947;[93] NICE TA927;[58] TA872;[6] TA895;[97] TA1048;[60] TA306;[98]TA649;[92] ID6202;[54] NG52.[96]

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First-line treatment

Following a positive NICE recommendation of Pola-R-CHP (polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone) as a 1L treatment for patients with LBCL with an IPI score of 2–5 in 2023 (TA874), UK CAR T Experts confirmed that the majority of patients now receive Pola-R-CHP as a 1L treatment.[50, 99]

Prior to the recommendation of Pola-R-CHP, 1L treatment for LBCL generally involved rituximab-containing immunochemotherapy regimens (historically R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone]), with or without radiotherapy.[36, 100, 101] In 2021, it was estimated that approximately 60–70% of patients were cured after receiving 1L R-CHOP, indicating DLBCL as a potentially curable disease.[48, 49]

Despite the curative intent of 1L treatment, approximately 30–40% of patients will not achieve cure at 1L.[11] Of those who do not achieve cure, an estimated 10–15% of patients with DLBCL develop primary refractory disease and the remaining 20–25% of patients will relapse after an initial response to 1L treatment.[48, 49] Patients who remain relapse free after two years are generally considered to have similar survival prospects to age- and sex-matched individuals in the general population, and are thus considered to be in long term remission.[102, 103]

Second-line treatment

Patient outcomes at 2L are notably worse than 1L. During clinician interviews that took place as part of this appraisal, UK CAR T Experts estimated that approximately 60–65% of patients will not achieve a cure at 2L and as a results will progress to later lines of therapy.[11] Treatment decisions in the 2L setting are dictated by timing of relapse and whether patients are suitable for ASCT, CAR T-cell therapy, or neither.

- Patients with LBCL who relapse ≤12 months after initial treatment, and are fit enough the receive ASCT, are considered suitable for CAR T-cell therapy at 2L. Liso-cel has recently been recommended by NICE for the treatment of relapsed (≤12 months) or primary refractory DLBCL, PMBCL, HGLCL and FL3B after 1L chemoimmunotherapy in adults who are suitable for ASCT, and represents routine practice at 2L in UK clinical practice.[60] In addition, patients with relapsed DLBCL (≤12 months) or primary refractory DLBCL who are eligible for ASCT may also 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.[97]
- For patients that relapse >12 months after 1L therapy, who are fit for ASCT, 2L salvage chemotherapy, followed by HDCT and ASCT is the preferred treatment option in UK clinical practice. Approximately 50% of patients with R/R DLBCL are deemed fit enough to receive HDCT and ASCT at 2L (no available data specifically for late relapses). Of the patients intended for transplant, only around half go on to 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) and as such, receive chemotherapy alone.[104] Clinical outcomes for patients who relapse <12 months are much worse than those for patient who relapse <12 months after 1L treatment with lower response rates (46% and 88%, respectively) and worse three-year event-free survival (20% and 45%, respectively) [51-53]
- For patients with R/R DLBCL who are not considered eligible for ASCT, glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) was recently recommended by NICE (ID6202) in November 2025 as an alternative treatment to polatuzumab vedotin plus rituximab and bendamustine (Pola-BR) or rituximab plus gemcitabine and oxaliplatin (R-GemOx).[54]

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- Finally, some patients may be treated with immunochemotherapy such as platinum- and/ or gemcitabine-based regimens.[36, 100, 105] However, the outcomes of these patients are very poor, with little chance of prolonged disease control.[106]

The NCCN guidelines recognise the transformative outcomes of CAR T-cell therapies and, as such, no longer recommend 2L ASCT in patients with early relapsed (≤12 months) or primary refractory LBCL.[72] Instead, the guidelines recommend liso-cel or axi-cel for suitable patients with relapsed LBCL (≤12 months) or primary refractory LBCL.[72]

Third-line and beyond treatment

Clinical practice at 3L+ is rapidly evolving in the UK, following the NICE recommendations for glofitamab (TA927), loncastuximab tesirine (TA947) and epcoritamab (TA954) within the last two years.[5, 93] The are therefore a number of potential treatment options for 3L+ patients, that include:[97]

- CAR T-cell therapy with axi-cel
- Bispecific antibodies (i.e. glofitamab and epcoritamab)
- Antibody-drug conjugates (i.e. Loncastuximab tesirine and polatuzumab vedotin)
- Immunochemotherapy (i.e. bendamustine, rituximab [Pola+BR])

Treatment choice at 3L+ is guided by a number of factors, including a patient's previous treatment history, and whether they are suitable and willing to receive intensive therapies, such as CAR T cell therapies.[5] For patients who have not yet received CAR T cell therapy, and are considered suitable to do so, treatment with axi-cel represents the main treatment option for patients in UK clinical practice. Patients suitable for CAR T-cell therapy may discontinue treatment prior to infusion due to disease progression or clinical decline. Drop-out rates for patients suitable for CAR T-cell therapy are currently 10–15%; however, these are anticipated to improve due to improved patient selection, alternative bridging therapies and faster manufacturing times.[11]

Patients requiring treatment at 3L+ are heavily pre-treated and therefore require effective 3L treatment options with tolerable safety profiles to minimise disease progression and prevent further relapse, whilst maintaining a reasonable QoL. The introduction of an additional alternative CAR T-cell therapies at 3L+, such as liso-cel, would provide clinicians with an alternative treatment option that offers comparable efficacy to existing CAR T-cell therapies (axi-cel) in the targeted population, while delivering more favourable safety outcomes. Clinicians would be able to select the best available CAR T-cell therapy for a given patient, considering disease kinetics, comorbidities, ability to tolerate high grade toxicities such as CRS and ICANS as well as patient, preferences including the desire to be treated in the outpatient setting.

B.1.3.4 Unmet need

As discussed in Section B.1.3.2, an LBCL diagnosis takes a significant toll on patient's HRQoL, which gets progressively worse with each relapse. For patients with R/R LBCL, both the HRQoL and emotional burden of disease is exacerbated with each line of treatment.[47] The introduction of bispecific antibodies and CAR T-cell therapies have been shown to be effective treatment options at 3L+ for those patients who are suitable to receive such treatments, with CAR T-cell therapies being the preferred option due to the availability of longer-term efficacy data.[107]

Axi-cel is currently the only CAR T-cell therapy available in the NHS for the targeted population in this submission.[6] Its introduction in the 3L+ setting was a step-change in the treatment pathway, providing a more efficacious treatment option compared with alternative 3L+ therapy options at the time (salvage chemotherapy and best supportive care). However, treatment with axi-cel is associated with a challenging toxicity profile which contributes to an increased treatment burden for patients.[60, 108] This represents a particularly high burden for a 3L+ patient population who are heavily pre-treated and

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where management of toxicities is often challenging. There is therefore still a large unmet need for alternative treatment options that provide a more favourable safety profile without compromising on efficacy.

Results of an MAIC (Section B.3.9) demonstrated the comparable efficacy and favourable safety profile of liso-cel compared with axi-cel. This was supported by UK CAR T Experts consulted as part of this submission who unanimously agreed that the evidence, so far, have been consistent in showing that liso-cel and axi-cel have comparable efficacy at 3L+.[11] In addition, CAR T Expert feedback in NICE TA1048 emphasised that the key difference between liso-cel and axi-cel was the safety profile, with patients receiving liso-cel experiencing fewer AEs compared with those receiving axi-cel, particularly in relation to CRS and neurotoxicity, including ICANS.[60] At the updated analysis of the ZUMA-1 trial, CRS occurred in 94 patients (93%), with Grade ≥3 cases in 11 patients (11%) and neurologic events (NE) occurred in 65 patients (64%) with Grade ≥3 events in 30 patients (30%).[109] This is consistent with French real-world data (RWD) from 2024 that reported [redacted]% and [redacted]% of patients receiving axi-cel at 2L and 3L, respectively, were admitted to ICU compared with only [redacted]% who were treated with liso-cel at 2L.[88, 89] Reducing pressure on ICUs is particularly critical in the UK, which has one of the lowest bed capacities among developed nations (Section B.1.3.2). Not only can ICU admission be distressing and detrimental to patient and caregiver HRQoL, it also exacerbates the economic burden on the NHS associated with the management of AEs following CAR T-cell therapy (see Section B.1.3.2). The introduction of a less toxic, but equally efficacious treatment options at 3L+, would aid in reducing some of the existing economic, HRQoL and resource burden.

The improved safety profile associated with liso-cel compared to axi-cel also allows for outpatient delivery of treatment, as demonstrated by the promising efficacy data from the outpatient delivery of liso-cel at 3L+ in TRANSCEND-OUTREACH-007 (see Section B.3.6.1.3).[110] This means that liso-cel has the potential to reduce capacity constraints by releasing inpatient hospital bed availability in UK hospitals. Treatment with liso-cel is therefore expected to alleviate some of the burden on healthcare resources, help optimise resource utilisation within the NHS, and improve the overall patient experience and outcomes.[60] This was supported by US RWD on patients with R/R LBCL who successfully received liso-cel in an outpatient setting between April 2022 and October 2024 (Section B.1.3.2).[14]

The cost-comparison analysis presented within this submission attempts to capture and quantify the additional cost savings associated with the improved safety profile of liso-cel compared with axi-cel. However, the ability to capture these benefits is limited, as AE management and in-hospital delivery costs are captured within a single CAR T tariff cost, applied to both treatments equally. As such, some of these benefits cannot be captured in the cost-comparison analysis, as discussed in Section B.2

Proposed positioning of liso-cel

The relevant population for this submission is aligned with the reimbursed population for axi-cel in 3L+ and comprises adult patients with R/R LBCL, specifically those who are suitable to receive CAR T-cell therapy at 3L+. This includes patients who:

- Relapsed <12 months after 1L treatment but did not receive ASCT due to ineligibility, then relapsed/progressed post 2L immunochemotherapy and are CAR T suitable at 3L+.
- Relapsed ≥12 months post 1L treatment and were eligible for 2L ASCT but did not respond to reinduction treatment and remain CAR T suitable at 3L+.
- Relapsed following 2L ASCT but are still deemed suitable to receive CAR T-cell therapy.

By 2027, BMS estimate that liso-cel will account for [redacted] of the market share of CAR T-cell therapy for patients who are suitable for CAR T-cell therapy at 3L+, with axi-cel shares decreasing from [redacted] in the same population.[111]

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B.1.4 Equality considerations

No equality issues relating to the use of liso-cel as a 3L+ treatment for patients with R/R LBCL have been identified or are anticipated.

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B.2 Key drivers of the cost effectiveness of the comparator(s)

Axi-cel has received a positive NICE recommendation in TA872 (in February 2023) for 3L+ R/R LBCL. This followed its initial recommendation for use within the CDF in TA559 (in January 2019).[6] This CDF exit process took place under the 2016 CDF exit guidelines, in which the technology was reappraised under the original decision problem and no changes to the scope of the original appraisal were allowed.[112] As such, greater emphasis on outcomes from NICE TA872 are given in the following sections.

B.2.1 Clinical outcomes and measures

For this submission, the cost-comparison analysis assumed comparable efficacy between liso-cel and axi-cel, based on a MAIC (see Section B.3.9), and supported by UK CAR T Experts consulted as part of this submission who unanimously agreed that the evidence, so far, have been consistent in showing that liso-cel and axi-cel have comparable efficacy at 3L+.[11] Therefore, no differences in clinical efficacy outcomes were reflected in the model. The analysis also assumed an improved safety profile, based on the MAIC. The following section provides an overview of the key clinical outcomes and measures considered in the cost-effectiveness evaluation submitted as part of the initial TA559 and the subsequent CDF review, TA872. A summary is provided in Table 4.

Of particular note, in the original appraisal of 3L+ axi-cel (TA559), individual AEs, including hypogammaglobulinaemia, were modelled explicitly. However, as part of TA872 (3L+ axi-cel) and TA895 (the appraisal of axi-cel for R/R LBCL after 1L chemoimmunotherapy), the CAR T tariff was introduced and ultimately included as the Committee's preferred approach in both appraisals.[6, 97] This tariff covers all care costs from the decision to proceed with CAR T-cell therapy up to 100 days post-infusion, including drug administration, resource use, and AE management—except for intravenous immunoglobulins (IVIg) treatment for hypogammaglobulinaemia and ICU admissions. As such, the Committee's preferred base case in TA872 consisted of a one-off cost of £41,101 for the first 100 days plus the costs of conditioning chemotherapy drugs, stem cell transplantation and IVIg, as these three costs are reimbursed separately by NHS England. The most recent CAR T tariff value, reflecting the 2025/26 financial year, is £60,462 (based on NICE ID6325 for brexucabtagene autoleucel [brexu-cel]).[113]

In this submission, only IVIg usage was modelled as a safety outcome, as the CAR T tariff covered all other AE costs (as noted above). Therefore, IVIg usage was the only relevant outcome to this appraisal of those listed in Table 4. Further details are provided in Section B.4.1.

The primary efficacy outcome from ZUMA-1 was ORR, defined as complete response (CR) or partial response (PR), as assessed by the investigator; however, this outcome was not included within the economic model supporting TA872.[6] Key secondary efficacy endpoints included ORR according to central review, PFS and OS; however, only PFS and OS outcomes, alongside safety outcomes, were included in the cost-effectiveness model of TA872.[6]

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Table 4: Clinical outcomes and measures appraised in NICE TA559 (STA; axi-cel) and TA872 (CDF review; axi-cel)[a]

Outcomes	Endpoint definition	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
ORR	Defined as CR or PR per IWG response criteria for Malignant Lymphoma as determined by the study investigators.	**No**	N/A	N/A	N/A
OS ZUMA-1 (updated analysis [DCO: August 2021])	Defined as the time from the infusion of axi-cel to the date of death from any cause.	**Yes**, with parametric survival curves (mixture cure models and flexible parametric models) fitted to the KM data to extrapolate beyond the trial duration.	OS was not a key driver in the model presented in TA872. The base case extrapolation for axi-cel (log-logistic [mixture cure model]) corresponded to an ICER of £49,159 at axi-cel PAS price. The scenario analysis extrapolation (2-knot normal) was associated with an ICER of £49,415 at axi-cel PAS price.	The Committee concluded that the Company's OS extrapolation modelling approach was appropriate.	The EAG highlighted that all extrapolations using mixture cure and spline models were higher than ZUMA-1 KM data from 50 months onwards. It argued that this was potentially overestimating long-term survival.
PFS ZUMA-1 (primary analysis [DCO: January 2017])	PFS according to the investigator's assessment, based on IWG 2007 criteria.	**Yes**, with parametric survival curves (standard parametric curves) fitted to the Kaplan-Meier (KM) data to extrapolate beyond the trial duration.	PFS extrapolations were not a key driver in the model presented in TA872. However, the Committee noted that other plausible extrapolations increased the ICER. The base case extrapolation for axi-cel (Gompertz) corresponded to an ICER of £49,159 at axi-	The Committee would have preferred longer-term progression data and flexible models considered in the base-case analysis. The Committee concluded that the company analysis was acceptable but associated with uncertainty.	The EAG had requested PFS data beyond 2 years, but the Company explained these data were not collected. The NICE technical team and EAG outlined that, given the heavy censoring in the PFS curve and low numbers at risk in the tail of the

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Outcomes	Endpoint definition	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
			cel PAS price. The scenario analysis extrapolation (log-logistic [mixture cure model) corresponded to an ICER of £49,802 at axi-cel PAS price.		curve, any plateau in PFS was still uncertain.
Intravenous immunoglobulins (IVIg) usage SACT Dataset	The proportion of patients who have IVIg treatment following axi-cel, and the length of time for which this is required.	**Yes**, IVIg inputs (percentage of people receiving IVIg, and IVIg treatment duration) were informed by SACT data.	IVIg use was not reported to be a key driver of cost-effectiveness and the EAG confirmed that the assumptions around IVIg usage had a minor impact on the ICER.	During technical engagement of TA872, the Company and EAG agreed to use available SACT data to inform IVIg inputs, which showed that around 16% of patients received IVIg for approximately 6.5 months following CAR T-cell therapy.	In TA559, the committee concluded that the need for IVIg treatment remained unknown, so the effect of B-cell aplasia on mortality risk was uncertain.
AEs[b] ZUMA-1 (primary analysis [DCO: January 2017])	N/A – No specific AEs defined by Committee.	**Yes**, AE costs were captured by the NHS England CAR T tariff.	AEs were not reported to be a key driver of cost-effectiveness.	The Committee highlighted that it was not appropriate to use the original NHS England CAR T tariff (from TA559) in the modelling because it is a mechanism for NHS England to fund hospitals to provide CAR T-cell therapy and is not designed for health technology evaluation. It also	NR

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Outcomes	Endpoint definition	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
				noted that the original tariff was not transparent and may have included costs that were not relevant to axi-cel at 3L. The Committee preferred the use of the CAR T tariff that was produced as part of TA895 (£41,101) to represent the costs associated with the administration of CAR T-cell therapies.[60]	
HRQoL ZUMA-1 (primary analysis [DCO: January 2017])	PROs were assessed using EQ-5D-5L in the safety management Cohort at screening, Week 4, Month 3 and Month 6 post axi-cel infusion.	**Yes**, a crosswalk algorithm was used to convert EQ-5D-5L to EQ-5D-3L (as preferred by NICE) and then a UK valuation algorithm was applied to convert EQ-5D-3L descriptive scores to the EQ-5D-3L index with UK population-based health utility values. The model also assumes that if patients remained in	The HSUVs for the PF and PD states were the second and third most influential parameters on cost-effectiveness in the model (range: ~£48,500, ~£53,000 and ~£48,000, ~£50,500 at axi-cel PAS price, respectively).	The Committee would have preferred scenarios investigating the impact of health state utility, but concluded that, as in the original appraisal, the economic model was appropriate for decision making.	The Committee questioned the assumption that people in remission returned to general population utility. The committee thought it would be more clinically valid for people in remission to have a utility decrement applied to account for the impact of having had DLBCL or PMBCL and intensive treatments.

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Outcomes	Endpoint definition	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
		the PFS state for 2 years, they are classed as being in long-term remission and are thus assumed to have equal utility values as the age and gender matched general population after this point.			

Footnotes: [a]All details were extracted from TA872 unless otherwise specified, given this was anticipated to represent the most up-to-date source of information. [b]Details extracted from TA559, as this topic was not discussed in TA872.
Abbreviations: AE: adverse event; CDF: Cancer Drugs Fund; CR: complete response; DCO: data cut-off; DLBCL: diffuse large B-cell lymphoma; EAG: external assessment group; EQ-5D-3L: euroqol 5-dimension 3-level; EQ-5D-5L: euroqol 5-dimension 5-level; HRQoL: health-related quality of life; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; IWG: International Working Group; KM: Kaplan Meier; N/A: not applicable; NICE: National Institute for Health and Care Excellence; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PF: progression-free; PD: progressive disease; PMBCL: primary mediastinal B-cell lymphoma; PR: partial response; PRO: patient-reported outcome; SACT: systemic anti-cancer therapy; STA: single technology appraisal; TA: technology appraisal; UK: United Kingdom.

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B.2.2 Resource use assumptions

Resource use and cost elements submitted as part of the initial NICE TA559 and the subsequent CDF review, NICE TA872, that are most relevant to the current evaluation are included in Table 5.

As noted above, the CAR T tariff is the primary input for capturing resource use and has been applied within the cost-comparison model (CCM) of this submission (Section B.4.2).[113] As such, the resource use and cost inputs included within this submission are in line with those included within NICE TA872, including the CAR T tariff and IVIg.[6] Additionally, ICU costs were include within the CCM, since they are excluded from the tariff and expected to differ between liso-cel and axi-cel.

The CCM aimed to account for cost differences expected between liso-cel and axi-cel. For resource use costs captured within the CAR T tariff, these were assumed equal for both treatments since a single tariff was applied to both arms. This assumption may have overestimated AE costs for liso-cel, given its more favourable safety profile.

Table 5: Resource use and cost elements submitted in NICE TA872 (CDF review; axi-cel) and a comparison against NICE TA559 (STA; axi-cel)

Costs	NICE TA872	Comments
Drug acquisition costs	Axi-cel and a salvage chemotherapy were included in the cost-effectiveness analysis. Costs associated with axi-cel were assumed to be a one-off cost including all shipping, engineering and generation of CAR T cells. Unit costs were derived from standard sources including the Drugs and pharmaceutical electronic market information tool (eMIT) and the NHS Reference Costs.[114, 115] In the updated analysis, the CAR T tariff was assumed to include the costs of leukapheresis and conditioning chemotherapy (IV cyclophosphamide and fludarabine).	Approach aligned with NICE TA559.
Drug administration costs	The Company considered each cost category individually and the Committee were satisfied that this captured a reasonable projection of the cost to the NHS of delivering CAR T-cell therapy.	In NICE TA559, axi-cel administration and subsequent monitoring were assumed to include the cost of an elective hospitalisation, in line with the NICE regenerative medicines report.[116] Administration of BSC was assumed to incur the cost of a non-elective hospitalisation.
Health state costs	Costs associated with the PFS and PD health states were considered within the model. It was assumed that patients remaining in the PFS health state for >2 years no longer incurred the cost of medical resource use of PFS, as they were considered to be in long-term remission. The costs associated with health care professionals, treatment follow-up and hospital resource use were captured by the NHS England CAR T tariff.	Approach aligned with NICE TA559.
AE costs	Costs associated with the management of AEs associated with axi-cel treatment, except hypogammaglobulinaemia (IVIg	In TA559, all costs were included in line with the NICE regenerative medicines report.[116]

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Costs	NICE TA872	Comments
	usage), were captured by the NHS England CAR T tariff, as noted in Section B.2.1.	
Miscellaneous costs	Costs associated with the training of healthcare professional in the use of axi-cel were captured by the NHS England CAR T tariff. Additional costs for allogeneic SCT were applied to patients in the axi-cel treatment arm as a number of patients in the ZUMA-1 trial underwent allogenic SCT following axi-cel infusion.	Approach aligned with NICE TA559.

Abbreviations: AE: adverse event; BSC: best supportive care; CAR T: chimeric antigen receptor T-cells; CRS: cytokine release syndrome; eMIT: electronic market information tool; HRG: Healthcare Resource Group; IV: intravenous; IVIg: intravenous immunoglobulin; NHS: National Health Service; PD: progressive disease; PFS: progression-free survival; SCT: stem cell transplant; TA: technology appraisal.
Source: NICE TA872.[6]

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B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant published data for the management of LBCL at 3L+.[117] Initial searches of the electronic databases were performed in April 2019 and searches updated in February 2021 and September 2025. Across the entire database search covering the period from 2003 to September 2025, a total of 191 eligible publications reporting on 13 unique studies were included.

See Appendix G for full details of the process and methods used to identify and select the clinical evidence relevant to the treatment being evaluated for the original SLR and all subsequent updates.

B.3.2 List of relevant clinical effectiveness evidence

Four clinical trials provide clinical evidence for liso-cel in patients with R/R LBCL at 3L+ (Table 6).

TRANSCEND-NHL-001 (NCT02631044)

The TRANSCEND-NHL-001 trial (herein referred to as TRANSCEND) is a Phase I, single-arm, open-label trial, conducted at 14 sites across the US, evaluating the efficacy and safety of liso-cel for the treatment of patients with R/R NHL at 3L+.[25, 118]

The trial assessed a DLBCL cohort and an MCL cohort. The DLBCL cohort included patients with DLBCL, PMBCL and FL3B, which is slightly broader than the target population for this submission. However, of the patients in TRANSCEND, only a small minority had FL3B, in line with the ~2% of patients who would be expected to have FL3B in UK clinical practice. The TRANSCEND patient population can therefore be considered generalisable to the targeted population within this submission (see Section B.3.3.6, Table 13).[40]

TRANSCEND is the primary source of evidence for liso-cel in patients with R/R LBCL at 3L+ in this submission, as it is the pivotal clinical trial used for the regulatory approval of liso-cel, providing information on 229 patients (DLBCL Cohort Treated Set; DL1+DL2) relevant to the NICE decision problem.[33]

- Full details of the TRANSCEND trial methodology are presented in Section B.3.3.2, with definitions of the analysis sets in Table 9.
- Data presented throughout Section B.3.6 and B.3.10 correspond to the final September 2021 data cut-off (DCO). Additional long-term follow-up (LTFU) data for OS and posttreatment-emergent AEs were collected at the January 2024 DCO (see Section B.3.3.2).
- All patients who underwent leukapheresis were included in the intent-to-treat (ITT) Leukapheresis Set (N=345). Any patients who received at least one dose of liso-cel were included in the DLBCL Cohort Treated Set (N=270). If a patient had PET-positive disease prior to liso-cel administration, they were included in the DLBCL Cohort Efficacy set (N=257; see Section B.3.3.3, Table 9).[33]
- All TRANSCEND results are presented for the combined DL1 and DL2 dosing regimen subgroup (DL1+DL2), to align with the approved dosing schedule for liso-cel in this indication (see Section B.3.3.1, Table 7).[1]
    - Efficacy results are presented for the DL1+DL2 DLBCL Cohort Efficacy Set (N=216) in Section B.3.6.1.
    - Safety results are presented for the DL1+DL2 DLBCL Cohort Treated Set (N=229) in Section B.3.10.1. The use of the Treated Set for safety analyses allows for the accurate assessment

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of adverse events directly related to the liso-cel treatment, is in line with previous NICE appraisals for similar treatment regimens (TA872 and TA677).[6, 119]

- Additional data, including sensitivity analyses of ORR and PFS, EORTC QLQ-C30 results and posttreatment-emergent AEs from the TRANSCEND clinical trial, are presented in Appendix J and within the CSRs provided in the reference pack accompanying this submission.[59, 120]

GC-LTFU-001 trial (NCT03435796)

The GC-LTFU-001 trial is an ongoing Phase II/III, multicentre, prospective study conducted across 182 sites across the 17 countries including the UK. The trial is a LTFU study collecting data on a variety of safety and efficacy outcomes for all paediatric and adult patients with MCL and DLBCL exposed to CAR T or other gene-modified (GM) T-cell therapy, who had participated in a previous BMS sponsored or BMS alliance partner sponsored study.

Patients from the TRANSCEND trial were eligible to enrol in the GC-LTFU-001 study if they had received at least one infusion of GM T-cells, and had discontinued, or completed the post-treatment follow-up period.[121, 122] [redacted] patients from the TRANSCEND study enrolled in GC-LTFU-001, and this study provides LTFU data on these patients for up to 15 years post-last dose of liso-cel.[59, 121]

- Full details of the GC-LTFU-001 trial methodology are presented in Appendix M.
- The study collected data on multiple outcomes of relevance to patients with NHL; however, only the long-term OS and posttreatment-emergent AE outcomes for patients from the TRANSCEND trial are relevant to this submission.
- Disease status was collected for patients who had not progressed on the parent study and survival status was collected for all surviving patients enrolled in this LTFU study. The data were combined with data from the corresponding parent study for analyses, as appropriate.
    - Combined longer-term OS data for TRANSCEND and GC-LTFU-001 are presented in Section B.3.6.2 (DCO: 31st January 2024).
- Posttreatment-emergent AE outcomes are presented in Section B.3.10.2.

TRANSCENDWORLD (NCT03484702)

The TRANSCENDWORLD trial is a Phase II, single-arm, multicentre, multicohort study conducted in 20 sites across 11 countries, including the UK.[123] This study was designed to determine the efficacy and safety of liso-cel given at a single dose of 100 x 10^6 CAR+ T-cells in an international population of adult patients, split in to five cohorts, as described in Table 6.

- Details of the TRANSCENDWORLD trial methodology are presented in Appendix K.
- Efficacy and safety results are reported for the Liso-cel Treated Set (N=[redacted]), which includes all patients who received liso-cel.
    - Within the Liso-cel Treated Set, only Cohort 1 (Table 6; n=[redacted]) is relevant to the decision problem in this submission and, therefore, efficacy and safety results from this cohort only are presented in Sections B.3.6.3 and B.3.10.3, respectively.

TRANSCEND-OUTREACH-007 (NCT03744676)

The TRANSCEND-OUTREACH-007 trial (herein referred to as OUTREACH) is a Phase II, single-arm, multi-centre trial, conducted in 23 sites across the US.[124] OUTREACH is a study modelled on the TRANSCEND study, specifically designed to evaluate the efficacy and safety of liso-cel in patients with 3L+ R/R LBCL across outpatient settings.

- Details of the OUTREACH trial are available in Appendix L.

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- A summary of efficacy and safety results for the DLBCL cohort (n=82) are presented in Sections B.3.6.4 and B.3.10.4, respectively.

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Table 6: Clinical effectiveness evidence

Study	TRANSCEND-NHL-001 (NCT02631044)[118]	GC-LTFU-001 (NCT03435796)[121]	TRANSCENDWORLD (NCT03484702)[123]	TRANSCEND-OUTREACH-007 (NCT03744676)[124]
Study design	Phase I, single-arm, open-label, multi-centre study	Ongoing, prospective LTFU study	Phase II, single-arm, open-label, multi-centre study	Phase II, single-arm, open-label, multi-centre study in the inpatient versus outpatient setting
Study dates	January 2016–May 2024	July 2018–November 2036	June 2023–December 2023	November 2018–September 2023
Population	Patients with R/R B-cell NHL, including DLBCL not otherwise specified (NOS), DLBCL transformed from indolent lymphoma, high-grade lymphoma (HGL) including DLBCL with double/triple hit, PMBCL, FL3B, and MCL. The trial population was assessed in two cohorts: • **DLBCL cohort**: Patients with DLBCL, PMBCL or FL3B who had received prior therapy with an anthracycline and rituximab (or other CD20-targeted agent) and had relapsed or refractory disease after at least two lines of therapy or after ASCT (ITT population; n=345). Within this cohort, [redacted] patients are considered of relevance to this submission (DL1+DL2 DLBCL Cohort Treated	Any paediatric or adult patient who had received at least one CAR T-cell therapy or other genetically engineered T cell product (GM T-cells) infusion as part of a previous Celgene-sponsored or Celgene alliance partner sponsored study.	• **Cohort 1:** DLBCL NOS (de novo or transformed follicular lymphoma), HGL (double hit lymphoma/triple hit lymphoma) and FL3B, ≥2 lines of therapy, including an anthracycline and a CD20-targeted agent (n=[redacted]) The following cohorts were included in the study but not considered relevant to the decision problem: • **Cohort 2:** Transplant-ineligible patients with DLBCL NOS (de novo or transformed from FL), HGL (double hit lymphoma/triple hit lymphoma) and FL3B, who failed first-line therapy including an anthracycline and a CD20-targeted agent • **Cohort 3:** Japanese patients only, meeting eligibility for Cohorts 1 or 2	Patients with R/R DLBCL who had received prior therapy with an anthracycline and rituximab (or other CD20-targeted agent) and had relapsed or refractory disease after at least two lines of therapy or after ASCT (N=82)[110]

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	Set)[a] • **MCL cohort**: Patients had at least one prior line of MCL therapy. This cohort is not presented as it is not relevant to the decision problem (n=[redacted]		• **Cohort 4**: Double hit lymphoma/triple hit lymphoma after one line of therapy • **Cohort 5:** Primary central nervous system lymphoma after at least one line of therapy including high-dose methotrexate • **Cohort 7:** Patients meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment	
Intervention(s)	Lisocabtagene maraleucel	N/A – LTFU study	Lisocabtagene maraleucel	Lisocabtagene maraleucel
Comparator(s)	N/A – single arm trial	N/A – single arm trial	N/A – single arm trial	N/A – single arm trial
Indicate if study supports application for marketing authorisation	Yes	No	Yes	No
Reported outcomes specified in the decision problem	• OS • PFS • Response rate • AEs of treatment • HRQoL	• Post-treatment-emergent AEs • OS All other endpoints were not considered a primary source of evidence in this submission.	N/A – Not considered a primary source of evidence in this submission	N/A – Not considered a primary source of evidence in this submission
All other reported outcomes	• DoR • Hospital resource use • PK, PC	N/A	• DoR • Event-free survival • Hospital resource use	• PC

Footnotes: [a]The number of patients in the DLBCL and MCL cohorts were taken from the May 2024 TRANSCEND CSR (September 2021 DCO).
Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; FL3B: follicular lymphoma grade 3B; HGL: high-grade lymphoma; HRQoL: health-related quality of life; MCL: mantle cell lymphoma; N/A: not applicable; NOS: not otherwise specified; OS: overall survival; PC: pharmacodynamics; PFS: progression-free survival; PK: pharmacokinetics; PMBCL: primary mediastinal B-cell lymphoma.

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Sources: BMS Data on File (TRANSCEND Clinical Study Report, 2024);[59] BMS Data on File (TRANSCENDWORLD Clinical Study Report Addendum 01, 2021);[125] Linhares et al. (2024);[110] clincaltrials.gov (NCT03744676);[124] clinicaltrials.gov (NCT03435796);[121] clinicaltrials.gov (NCT02631044);[118] clinicaltrials.gov (NCT03484702);[123] Abramson et al. (2024).[122]

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B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

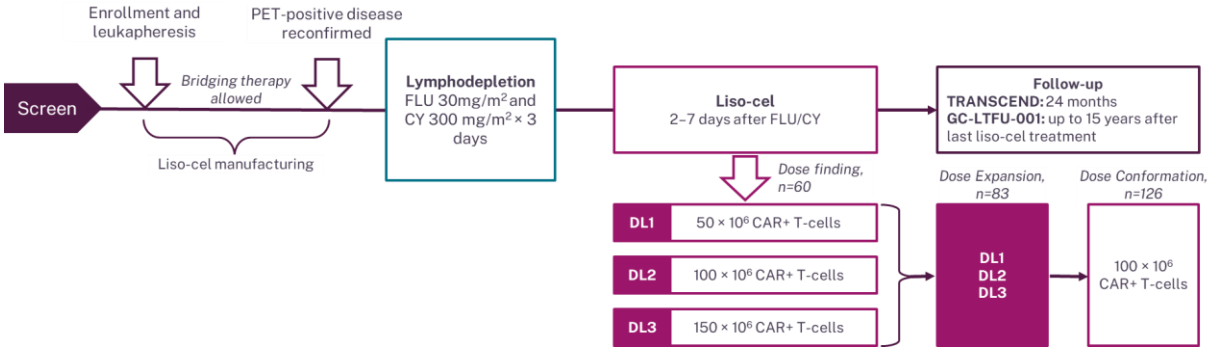
B.3.3.1 TRANSCEND trial design

TRANSCEND is a Phase I, single-arm, open-label, multicentre multicohort study conducted in the US to determine the safety, antitumour activity, and pharmacokinetics of liso-cel in adult patients with R/R B-cell NHL.

Two disease-specific cohorts were enrolled: the DLBCL cohort (n=270) and the MCL cohort (n=[redacted]. As only the DLBCL cohort is relevant to the decision problem, only data from this cohort are presented throughout this submission.

The DLBCL cohort included patients with DLBCL NOS (*de novo* or transformed from indolent lymphoma), HGL, PMBCL, and FL3B who had received at least two prior lines of therapy.[59, 118] The TRANSCEND study design is outlined in Figure 4.

Figure 4: TRANSCEND study design



Footnotes: [a], DL1 was also tested as a two-dose regimen, with a second dose of liso-cel given 14 days after the first dose.
Abbreviations: CAR: chimeric antigen receptor; CY: cyclophosphamide; DL: dose level; FLU: fludarabine; PET: positron emission tomography.
Source: BMS Data on File (TRANSCEND Clinical Study Report, April 2019).[126]

Study procedure

Following enrolment, leukapheresis was conducted to collect cells from each patient to enable liso-cel product manufacture. If necessary, anticancer therapy (i.e., bridging therapy) was allowed to stabilise the patient's disease whilst liso-cel was being manufactured. Where bridging therapy was used, positron emission tomography (PET)-positive disease had to be reconfirmed prior to beginning the treatment phase.[126]

During the treatment phase of the study, patients received lymphodepleting chemotherapy (LDC) with fludarabine and cyclophosphamide daily for three days. Between two and seven days after LDC, patients received liso-cel as two sequential infusions of $CD8^+$ and $CD4^+$ CAR^+ T cells, at one of three target dose levels:

- **Dose Level 1 (DL1)**: 50 × 10^6 CAR+ T cells (25 × 10^6 CD8+ CAR+ T cells and 25 × 10^6 CD4+ CAR+ T cells); single and 2-dose regimens tested: **DL1S** and **DL1D**, respectively
- **Dose Level 2 (DL2)**: 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells); single-dose regimen only: **DL2S**
- **Dose Level 3 (DL3)**: 150 × 10^6 CAR+ T cells (75 × 10^6 $CD8^+$ CAR^+ T cells and 75 × 10^6 CD4+ CAR+ T cells); single-dose regimen only: **DL3S**

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In the single-dose schedules (DL1S, DL2S and DL3S), liso-cel was administered 2 to 7 days after completion of LDC. In the two-dose schedule (DL1D), patients received the first dose as described above, and a second dose of liso-cel was given 14 days after the first dose of liso-cel (without further LDC between the two doses).

Throughout the submission, results are presented for the combined DL1+DL2 dosing regimen subgroup of the DLBCL Cohort Treated Set (N=229) and DLBCL Cohort Efficacy Set (N=216). This is the most relevant subgroup for decision-making as it is aligned with the approved dosing schedule for liso-cel in this indication (Table 7).[1] Only the single dose schedules (DL1S and DL2S) are directly aligned with the marketing authorisation for liso-cel in this indication. However, the outcomes for patients receiving the DL1D dosing regimen are expected to be generalisable to patients receiving the DL1S dosing regimen, given no efficacy differences have been observed between the two dose levels.[120] Additionally, only a small minority of patients received the DL1D dosing regimen (n=[redacted]) within the DL1+DL2 subgroup (N=229; DLBCL Cohort Treated Set).[25, 59, 122]

The results from DL3 are not considered relevant to this submission as this dosing regimen of liso-cel is not authorised in this patient population (Table 7).[1] Results for all individual dose levels are presented in the CSRs provided within the reference pack.[59]

Table 7: Dosing regimens received by patients in the TRANSCEND trial (DLBCL Cohort Treated Set; 28th September 2021 DCO)

Dose received in trial[a]	Included within marketing authorisation (Yes/No)	Relevant to NICE decision problem (Yes/No)
DL1+DL2 (n=229)		
DL1S (n=45)	Yes	Yes
DL1D (n=[redacted])	No	Yes[b]
DL2S (n=178)	Yes	Yes
DL3S (n=41)	No	No

Footnotes: [a]DL1 = 50 × 10^6 CAR+ T cells; DL2: 100 × 10^6 CAR+ T cells; DL3: 150 × 10^6 CAR+ T cells. In DL1D a second dose of liso-cel was given 14 days after the first dose of liso-cel. Patient numbers are based on the DLBCL Cohort Treated Set at the September 2021 DCO. [b]As noted above, results in this submission are presented for the combined DL1+DL2 dosing regimen. Although the DL1D dosing regimen is not included within the MHRA licence for liso-cel, the outcomes for these patients are expected to be generalisable to patients receiving the DL1S dosing regimen, given no efficacy differences have been observed between the two dose levels.
Abbreviations: DL: dose level; NICE: National Institute for Health and Care Excellence.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, 2021);[120] Liso-cel SmPC[2]

Patients could receive more than one dose of liso-cel in the TRANSCEND trial, but only under three prespecified situations:

- Two-dose schedule (DL1D): This was a protocol-defined schedule into which a patient may have been assigned at study enrolment, scheduled to receive two doses of liso-cel approximately 14 days apart (n=[redacted] patients receiving the DL1+DL2 regimen were included in the DL1D dosing regimen)
- Retreatment cycles: Subsequent liso-cel cycles may be administered if PD occurred following CR to liso-cel (No patients receiving the DL1+DL2 regimen underwent retreatment cycles)
- Additional cycles: Additional liso-cel cycles may have been administered to a patient only if stable disease or PR was their best overall response (BOR) after the initial response assessment. A total of [redacted] patients underwent additional cycles, [redacted] of these underwent two cycles and [redacted] underwent three cycles.

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At the end of the treatment phase (Day 29) patients were assessed. After this, patients entered the LTFU period and were monitored for safety, disease progression, and survival at approximately 3, 6, 9, 12, 18, and 24 months post-last dose of liso-cel, including after disease progression or initiation of additional anticancer therapies (Figure 4).

B.3.3.2 Trial methodology

The TRANSCEND trial methodology is summarised in Table 8. The primary endpoints of the trial were ORR and AEs, with other safety and survival outcomes measured as secondary endpoints (HRQoL, response rates, PFS, OS). Additional PK and pharmacodynamic exploratory endpoints were also assessed in the TRANSCEND trial; however, these have not been presented within this submission and are instead available in the May 2024 TRANSCEND clinical study report (CSR).[59]

Table 8: Summary of TRANSCEND trial methodology

Trial name	**TRANSCEND (NCT02631044)**
Location	US (14 sites)
Trial design	An open-label, multicentre, single-arm, Phase 1 study to determine the safety, PK, and antitumor activity of liso-cel in adult patients with R/R NHL (DLBCL, PMBCL, FL3B and MCL)
Eligibility criteria for participants	• Patients (aged ≥18 years) with R/R DLBCL NOS (includes transformed DLBCL from iNHL, HGL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology16, PMBCL, and FL3B) • Patients must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have R/R disease after at least two lines of therapy or after ASCT • PET-positive disease according to the 'Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification'.[127] • ECOG PS of 0 or 1 • Adequate organ (adequate bone marrow function to receive LDC, creatine clearance (CrCl) >30 mL/min/1.73 m2, ALT ≤5 x ULN and total bilirubin <2.0 mg/dL), pulmonary (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1 dyspnoea and SaO_2 ≥92% on room air), and cardiac (LVEF ≥40%) function • Adequate vascular access for leukapheresis procedure (either peripheral line or surgically placed line) • Patients who received previous CD19-targeted therapy must have had CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy Full inclusion and exclusion criteria for the TRANSCEND trial can be found in the TRANSCEND protocol provided within the reference pack accompanying the submission.[128]
Intervention	Liso-cel
Comparator	N/A – Single-arm trial
Method of study drug administration	Prior to treatment with liso-cel, patients were treated with LDC (fludarabine 30 mg/m^2/day plus cyclophosphamide 300 mg/m^2/day for three days). Patients were then premedicated with 650 mg oral (PO) acetaminophen and 25–50 mg diphenhydramine hydrochloride or, equivalent antihistamine (PO or IV) 30 to 60 minutes prior to liso-cel administration. Patients then received liso-cel through sequential IV infusions of CD8+ and CD4+ CAR T-cells, according to the assigned dose regimen (Table 7):

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	• **DL1: 50 × 10^6 CAR^+ T cells (single** and two-dose regimens: **DL1S** and DL1D) • **DL2: 100 × 10^6 CAR^+ T cells (single dose regimen: DL2S)** • DL3: 150 × 10^6 CAR^+ T cells (single-dose regimen: DL3S)
Permitted and disallowed concomitant medication	**Permitted:** • Red blood cells and platelet transfusions, and/or colony-stimulating factors • Prophylactic or empiric anti-infective agents • Physiologic replacement dosing of steroids • Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis **Prohibited:** • Steroids[a] • DLI[a] • GVHD therapies • Anticancer agents, excluding lymphodepleting conditioning chemotherapy and agents used for treatment of uncontrolled liso-cel proliferation, severe cytokine release syndrome (sCRS), or progression of lymphoma • Cetuximab, or other anti-eGFR treatments, unless indicated for treatment of uncontrolled liso-cel proliferation or sCRS • Experimental agents[a] • Radiation[a]
Primary outcome(s)	• The safety of liso-cel in adult patients with R/R B-cell NHL was evaluated through the type, frequency and severity of AEs Primary endpoints are defined in B.3.6.1.2.
Secondary outcomes	• CR rate • DoR • PFS • OS • HRQoL (EORTC-QLQ-C30 and EQ-5D-5L) • Pharmacokinetics • Numbers of ICU inpatient days and non-ICU inpatient days and reasons for hospitalisation Secondary endpoints are defined in B.3.6.1.3.
Exploratory endpoints (relevant to the submission)	N/A
Pre-planned subgroup analyses	In the DLBCL Cohort Efficacy Set, efficacy subgroup analyses were performed on the following variables • Age (<40 or ≥40 to <65 or ≥65 years; <65 or ≥65 years; <75 or ≥75 years) • Sex (male or female) • Ethnicity (Hispanic or Latino or not) • Race (White or Other) • Prior HSCT (yes or no) • Prior response status (refractory or relapsed to last prior therapy)[b] • Prior chemoresponse status (chemorefractory versus chemosensitive to last prior chemotherapy-containing therapy)[c] • CNS disease status (known disease or no known CNS)

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	• Cell of origin (geminal centre B-like [GCB] or non-GCB)
Duration of study and follow-up	• See Section B.3.3.5,Table 11 • Data from the primary and secondary DCOs (12th April 2019 and 12th August 2019, respectively) represent a median follow-up time of [redacted] months and [redacted] months, respectively • The final DCO (28th September 2021) provides the final analysis for ORR, PFS and DoR with a [redacted] month follow-up, as well as data on HRQoL and TEAEs • Data from the GC-LTFU-001 study (DCO: 31st January 2024) provides long-term OS data with a follow-up of [redacted] months, and details of posttreatment-emergent AEs

Footnotes: [a]Prohibited unless used as an anticancer agent after progression of lymphoma. [b]The status was refractory if a patient achieved less than a CR to last prior therapy; otherwise the status was relapsed. [c]The status was chemorefractory if a patient achieved SD or PD to last chemotherapy-containing regimen or relapsed <12 months after auto-HSCT; otherwise the status was chemosensitive.
Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; ASCT: autologous stem cell transplant; BCL2/6: B-cell lymphoma gene 2/6; CNS: central nervous system; CR: complete response; CrCl: creatine clearance; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; DL: dose level; DLBCL: diffused large B-cell lymphoma; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: epidermal growth factor receptor; FL3B: follicular lymphoma grade 3B; GCB: geminal centre B-like; GVHD: graft-versus-host disease; HGL: high-grade lymphoma; HRQoL: health-related quality of life; HSCT: hematopoietic stem cell transplant; IV: intravenous; LDC: lymphodepleting chemotherapy; LVEF: left ventricular ejection fraction; MCL: mantle cell lymphoma; MYC: myelocytomatosis oncogene; N/A: not applicable; NCI: National Cancer Institute; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; ORR: overall response rate; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; PMBCL: primary mediastinal B-cell lymphoma; PO: orally; PR: partial response; R/R: relapsed/refractory; SaO2: oxygen saturation; sCRS: severe cytokine release syndrome; ULN: upper limit of normal; US: United States.
Source: BMS Data on File (TRANSCEND protocol);[128] BMS Data on File (TRANSCEND Clinical Study Report, April 2019);[126] BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, 2021).[120]

B.3.3.3 Analysis sets

A total of four analysis sets were included within the TRANSCEND trial. Definitions for each of the analysis sets are presented in Table 9.

In this submission, efficacy results (Section B.3.6) are presented for the DLBCL Cohort Efficacy Set, and safety results (Section B.3.10) are presented for the DLBCL Cohort Treated Set, unless otherwise specified.

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Table 9: Analysis set definitions

Analysis set[a]	Definition	DCOs	Use in submission
DLBCL Cohort Leukapheresis Set (ITT; Total: N=345; DL1+DL2: [redacted])	All patients who had provided informed consent, who met all inclusion/exclusion criteria, and who underwent leukapheresis. This analysis set included patients treated with nonconforming products as well as those who received no treatment following leukapheresis (Figure 5, Section B.1.1.1)	• 12th April 2019 • 12th August 2019 • 28th September 2021 (presented in this submission for deaths)	The DL1+DL2 ITT population was used for the safety analysis of death incidence in TRANSCEND, in order to capture all deaths related to liso-cel treatment (N=[redacted]; Section B.3.10.1.3)
DLBCL Cohort Treated Set (Total: N=270; DL1+DL2: N=229)	All patients who received at least one dose of liso-cel (excluding patients who received nonconforming products as their first dose). If a patient received multiple liso-cel doses, the first dose of liso-cel should have been conforming product,[b] which met specification at the time of product release.	• 12th April 2019 • 12th August 2019 • 28th September 2021 (presented in this submission for TEAEs) • GC-LTFU-001: 31st January 2024 (presented in this submission for posttreatment-emergent AEs)	All safety results, other than deaths, are presented for the DL1+DL2 dosing regimen of the DLBCL Cohot Treated Set (N=229; Section B.3.10.1)
DLBCL Cohort Efficacy Set (Total: N=257; DL1+DL2: N=216)	All patients in the Treated Set who received at least one dose of liso-cel and who had PET-positive disease before liso-cel administration, based on IRC assessment.	• 12th April 2019 • 12th August 2019 • 28th September 2021 (presented in this submission for ORR, PFS, DoR and HRQoL) • GC-LTFU-001: 31st January 2024 (presented in this submission for OS)	Efficacy results are presented for the DL1+DL2 dosing regimen of the DLBCL Efficacy Set (N=216; B.3.6.1)
DLBCL Cohort Primary Analysis Set (N=[redacted])	Patients in the dose-finding, dose-expansion and dose-confirmation groups who failed at least two therapies in the DLBCL Cohort with DLBCL NOS (de novo or transformed from follicular lymphoma), or HGL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, treated with the DL2S)	• 12th April 2019 • 12th August 2019	Results for this analysis set are not presented in this submission.

Footnotes: [a] The patient numbers for each analysis set are based off the final analysis for each endpoint (September 2021 DCO: response rates, ORR and PFS; May 2024 DCO: OS, posttreatment-emergent AEs). [b] A nonconforming product is defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel, but was considered appropriate for infusion. **Abbreviations:** AE: adverse events; BCL2/6: B-cell lymphoma gene 2/6; CT: computed tomography; DCO: data cut-off; DL: dose level; DoR: duration of response; HRQoL: health-related quality of life; IRC: Independent Review Committee; HGL: high-grade lymphoma; ITT: intent-to-treat; MYC: myelocytomatosis oncogene; NOS: not otherwise specified; ORR: overall response rate; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; TEAE: treatment-emergent adverse events. **Source:** BMS Data on File (TRANSCEND Protocol);[128] BMS Data on File (TRANSCEND Clinical Study Report, May 2024);[59] Liso-cel SmPC;[1] Abramson et al. (2024).[122]

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B.3.3.4 Participant flow

A summary of the patient flow for TRANSCEND is presented in Figure 5 and Appendix J.

Figure 5: Summary of the patient flow for TRANSCEND (DCO: 28th September 2021)

Footnotes: [a] One patient had nonconforming product (CD8+ component nonconforming) manufactured following the first leukapheresis and subsequently had conforming product manufactured following a second leukapheresis 5 weeks after the first leukapheresis, but patient discontinued from the study prior to receiving liso-cel due to rapidly deteriorating clinical status. One patient received anticancer therapy for disease control and subsequently decided to undergo alternative treatment (n=1). Three patients no longer met the trial eligibility criteria. One patient withdrew consent. Two patients were not eligible for liso-cel infusion; [b] Liso-cel is composed of a target dose of CD8+ and CD4+ CAR T-cells, and each of these components was required to meet quality specifications. Nonconforming product refers to product that did not meet the specifications of liso-cel (e.g. one of the CD8+ or CD4+ cell components did not meet one of the requirements to be considered liso-cel); [c] Patients who were treated with product manufactured using the original manufacturing process (n=3).
Abbreviations: CAR: chimeric antigen receptor; IRC: independent review committee; LBCL: large B-cell lymphoma; LDC: lymphodepleting chemotherapy; PET: positron emission tomography.
Source: Abramson et al. (2020);[25] Abramson et al. (2024).[122]

At the September 2021 DCO, [redacted] patients ([redacted]%) in the DLBCL Cohort Treated Set (DL1+DL2) had completed the study and none were ongoing. At this DCO, [redacted] patients [redacted]%) had discontinued the study with [redacted] patients ([redacted]%) discontinuing due to death. The median on-study duration of follow-up (time from liso-cel infusion to the earliest of date of death, date last known alive, or DCO date) was [redacted] months. Full details of patient disposition are presented in Table 10.

Table 10: Patient disposition summary (DLBCL Cohort Treated Set; 28th September 2021 DCO)

Study status	DL1+DL2 (N=229)
Completed study	[redacted]
Discontinued from study	[redacted]
Patient withdrew consent	[redacted]
Study termination by sponsor	[redacted]
Lost to follow-up	[redacted]
Death	[redacted]
Other[a]	[redacted]
Consented to LTFU study	[redacted]

Footnotes: [a] Patient in hospice care with clinical status deteriorating rapidly. **Abbreviations:** DL: dose level; DLBCL: diffuse large B-cell lymphoma; LTFU: long-term follow-up. **Source:** BMS Data on File (TRANSCEND Clinical Study Report, May 2024).[59]

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B.3.3.5 Data cuts

A total of four analyses have been conducted on the TRANSCEND trial, including one analysis incorporating data from the GC-LTFU-001 trial (Table 11 and Table 12).

Table 11: Data cuts in TRANSCEND

Analysis	DCO	Presented in submission? (Yes/No)	Description
Primary analysis	12th April 2019	No	Conducted in the primary analysis set (n=[redacted]), to focus on the benefit/risk of liso-cel in a well-defined, homogenous DLBCL patient subpopulation of the DLBCL Cohort Treated Set (n=[redacted]).[126]
Updated analysis	12th August 2019	No	Conducted in the DLBCL Cohort Efficacy Set (n=[redacted])[a] and the DLBCL Cohort Treated Set (N=[redacted])[a] in response to health authority feedback received in September 2018, to provide an understanding of the totality of data in all types of LBCL patients treated with liso-cel, reflective of the full eligibility criteria for the study.[129]
Final analysis	28th September 2021	Yes	Provided updated analyses for both the DLBCL Cohort Efficacy Set (total: N=257; DL1+DL2: N=216)[a] and DLBCL Cohort Treated Set (total: N=270; DL1+DL2: N=229)[a].[120]
LTFU	31st January 2024	Yes	A total of [redacted] patients who completed the TRANSCEND trial were enrolled onto the GC-LTFU-001 study. At this DCO, TRANSCEND and GC-LTFU-001 data were combined to provide updated OS data (DLBCL Cohort Efficacy Set; total: N=[redacted]; DL1+DL2:[redacted]) and posttreatment-emergent AE data (DLBCL Cohort Treated Set; N=249).[b] Patients in TRANSCEND who did not enrol on the GC-LTFU-001 were censored at this DCO.

Footnotes: [a]The discrepancy in patient numbers between DCOs is a result of n=1 additional patient being treated between the August 2019 (DLBCL Cohort Treated Set, n=256) and September 2021 (DLBCL Cohort Treated Set, n=257) DCOs. [b]Posttreatment-emergent AEs were not reported by individual dose levels and, therefore, are presented for the full cohort.
Abbreviations: AE: adverse event; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; LPLV: last patient last visit; LTFU: long-term follow-up; MCL: mantle cell lymphoma.
Sources: BMS Data on File (TRANSCEND Clinical Study Report, April 2019);[126] BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021);[120] BMS Data on file (TRANSCEND Clinical Study Report, May 2024);[59] Abramson et al. (2024)[122]

Throughout the submission, data presented from the most recent DCO from which they are available (28th September 2021) except for OS and posttreatment-emergent AEs, which includes LTFU data from GC-LFTU-001 (DCO: 31st January 2024; Table 12). This provides the longest follow-up available and includes patients with DLBCL, PMBCL and FL3B as specified in the licensed indication. For each endpoint, results are presented for the DL1+DL2 combined dosing regimens, to align with the marketing authorisation for liso-cel in this indication (see Section B.3.3.1, Table 7).[1]

Table 12: TRANSCEND DCO dates for data presented within the submission

Outcome	Analysis performed at DCO	
	28th September 2021[120, 122]	31st January 2024[59]
Primary endpoint		

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Outcome	Analysis performed at DCO	
	28th September 2021[120, 122]	31st January 2024[59]
ORR	Yes	No
Secondary endpoints		
CR rate	Yes	No
DoR	Yes	No
PFS	Yes	No
OS	Yes	Yes (LTFU data)[a]
HRQoL	Yes	No
Safety		
AE	Yes	Yes (LTFU data)[b]

Footnotes: [a]LTFU data collected in the GC-LTFU-001 trial. [b]LTFU data for AEs report on posttreatment-emergent AEs only.
Abbreviations: AE: adverse event; CR: complete response; DCO: data cut-off; DoR: duration of response; HRQoL: health-related quality of life; LTFU: long-term follow-up; ORR: overall response rate; OS: overall survival; PFS: progression-free response.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, 2021 – Table 5.3.2-1 and Table 5.3.3.1-1);[120] BMS Data on File (TRANSCEND Clinical Study Report, May 2024);[59] Abramson et al. (2024).[122]

B.3.3.6 Baseline characteristics

A summary of key demographics and baseline characteristics for the DLBCL Cohort Treated Set (N=229) at the 28th September 2021 DCO is shown in Table 13.[120] The baseline characteristics are reported for the DLBCL Cohort Treated Set (n= 270; all patients who received at least one dose of liso-cel) as this includes all patients included in both the efficacy and safety analyses (see Table 3 for analysis set definition). A full table of baseline demographic and disease characteristics can be found in the TRANSCEND Addendum 01 2021 CSR provided in the reference pack.[120]

The patients receiving the DL1+DL2 dosing regimens in the DLBCL Cohort Treated Set (N=229) had a median age of 62.0 years, with 89 patients (38.9%) aged 65 or greater and 19 patients (8.3%) aged 75 or greater. This is similar to the median age observed for patients with R/R NHL treated with CAR T-cell therapies in the UK between December 2018 and January 2020 (58 years (range: 18, 75).[130] Although this study does not specify that the patients were 3L+, the only available CAR T-cell therapies recommended in the UK at the time of this study were those used at 3L+ (i.e. axi-cel).[6]

Patients were predominantly male (n=153; 66.8%).[1, 63] At screening, most patients in this group had an ECOG performance status (PS) of 1 or 0, with four patients (1.7%) having an ECOG PS of 2 at screening. Renal function impairment prior to LDC, defined as CrCl <60 mL/min, was reported in [redacted] patients ([redacted]%), and reduced cardiac function at screening, defined as LVEF ≥40% to <50%, in [redacted] patients ([redacted]%).

Table 13: Summary of baseline demographic and disease characteristics (DLBCL Cohort Treated Set)

Demographic	DL1+DL2 (N=229)
Age, years	
Median (range)	62.0 (18, 82)
Age group, n(%)	
<65 years	[redacted]
≥65 years	89 (38.9)

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Demographic	DL1+DL2 (N=229)
<75 years	[redacted]
≥75 years	19 (8.3)
Sex, n (%)	
Male	153 (66.8)
Race, n (%)	
American Indian or Alaska Native	[redacted]
Asian	[redacted]
Black or African American	[redacted]
Multiple	[redacted]
White	[redacted]
Not reported	[redacted]
Type of B-cell NHL, n (%)	
DLBCL NOS	117 (51.1)
HGL, including double/triple hit	33 (14.4)
DLBCL transformed from indolent lymphoma	60 (26.2)
FL3B	4 (1.7)
PMBCL	15 (6.6)
If DLBCL, cell of origin, n (%)	
GCB	[redacted]
Non-GCB	[redacted]
Unknown	[redacted]
Refractory or relapsed, n (%)[a]	
Refractory	186 (81.2)
Relapsed	43 (18.8)
Chemorefractory or chemosensitive, n (%)[b]	
Chemorefractory	160 (69.9)
Relapsed <12 months after ASCT	[redacted]
Last chemotherapy	[redacted]
Chemosensitive	[redacted]
Active CNS disease at first liso-cel infusion, n (%)	
Yes	6 (2.6)
No	[redacted]
Best prior response, n (%)[c]	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
LDH prior to LDC, n (%)	
≥500 U/L	[redacted]

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Demographic	DL1+DL2 (N=229)
<500 U/L	[redacted]
SPD per IRC prior to LDC, n (%)	
≥50 cm	[redacted]
<50 cm	[redacted]
Prior treatment, n (%)[f]	
HSCT	[redacted]
Allogenic	[redacted]
Autologous	[redacted]
Radiotherapy	[redacted]
Systemic therapy	[redacted]
Number of prior systemic treatments, n (%)	
Median (range)	3.0 (1, 8)
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
≥5	[redacted]

Footnotes: [a] Relapsed vs Refractory is defined as best response of CR vs best response of PR, SD, or PD to last systemic or transplant treatment with curative intent. [b] Chemorefractory is defined as experiencing SD or PD to last chemo-containing regimen or relapsed <12 months after auto-HSCT; otherwise it is chemosensitive. [c] Best prior response is the best response to any prior therapy. [d] Eligible diagnosis is defined as a patients LBCL diagnosis which met eligibility for the clinical trial. The date of this diagnosis captured in the database is used for calculating the time from diagnosis. If a patient had previous indolent lymphoma (eg follicular lymphoma), the date of the qualifying transformation diagnosis (e.g. tFL) was used, not the initial indolent lymphoma diagnosis date. [e] Percentages are based on number of patients with non-missing results. [f] Only regimens post diagnosis of DLBCL are included. Anticancer therapy for disease control was not counted as a prior systemic regimen unless the outcome was CR.
Abbreviations: ALC: absolute lymphocyte count; ASCT: autologous stem cell transplant; CNS: central nervous system; CR: complete response; CrCl: creatine clearance; CRP: C-reactive protein;DL: dose level;; DLBCL: diffuse large B-cell lymphoma; FL3B: follicular lymphoma grade 3B; GCB: germinal centre B-cell; HGL: high-grade lymphoma; HSCT: hematopoietic stem cell transplant; LDC: lymphodepleting chemotherapy; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; ND: not done; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; PD: progressed disease; PMBCL: primary mediastinal large B-cell lymphoma; PR: partial response; SD: stable disease; SPD: um of product of perpendicular diameters.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, 2021 – Table 5.3.1-1, Table 5.3.2-1 and Table 5.3.3.1-1);[120] Liso-cel SmPC.[1]

The baseline characteristics reported in the TRANSCEND trial are also broadly aligned to those reported in the ZUMA-1 trial (axi-cel), a trial population that was considered to be generally reflective of patients in UK clinical practice that would be suitable for CAR T-cell therapy by the EAG in NICE TA872.[6] As discussed in Section B.3.9.3, key factors were similar between trials; patients in the ZUMA-1 trial had a median age of 58 years, were predominantly male (n=68; 67%) and had an ECOG PS at baseline of 1 (n=59; 58%). Differences were observed for disease stage, tumour burden, extranodal disease, number of prior lines of therapy, prior auto-HSCT, bridging therapy, and R/R to last therapy when comparing the efficacy datasets.

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B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The definitions of the key primary, secondary and exploratory efficacy endpoints from the TRANSCEND trial presented in this submission are outlined in Appendix J.2.1. All efficacy endpoints have been presented from the most recent DCO from which they are available (28th September 2021) except for OS and posttreatment-emergent AEs, which include long-term follow-up data from GC-LFTU-001 (DCO: 31st January 2024; Table 12).

Efficacy and safety analyses were performed in accordance with a detailed Statistical Analysis Plan.[131] A summary of the statistical analysis methods used in the trial are presented in Table 14.

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Table 14: Statistical methods for the primary analysis (DLBCL Cohort)

Hypothetical objective	The trial tested the following hypotheses: • For the primary efficacy endpoint, that ORR >40% against the null hypothesis that the ORR ≤40% at a 1-sided 1% and 2.1% level of significance at the interim and primary analysis, respectively, powered for ORR=65% • For the primary analysis of ORR for chemorefractory patients based on the primary analysis set, the null hypothesis was ORR ≤30% and an alternative hypothesis was ORR >30% with the effect size of 25% (ORR=55%) • For the efficacy endpoint of CR rate, the null hypothesis was CR rate ≤0% and an alternative hypothesis was CR rate >20% with the effect size of 20% (CR rate=40%) • For the efficacy endpoint of CR rate for chemorefractory patients based on the primary analysis set, the null hypothesis was CR rate ≤10% and an alternative hypothesis was CR rate >10% with the effect size of 20% (CR rate=30%)
Statistical analysis	The one-sided significance level for the interim and primary analyses was planned to be 0.01 and 0.021, respectively, using the interpolated spending function (calculated using EAST v6.3.1). The overall one-sided type I error is 0.025. The interim analysis was not performed so all the alpha was be kept for the primary analysis. In accordance with the Statistical Analysis Plan, an interim analysis was planned when: • ≥75 patients in the primary analysis set had been treated at one recommended regimen across the dose-finding, dose-expansion and dose-confirmation groups; • The first 50 patients treated in the dose confirmation group of the primary analysis set had been followed for ≥3 months, or until death, disease progression, or withdrawal from the study; and • ≥20 patients treated in the dose confirmation group of the primary analysis set had been followed for ≥6 months or until death, disease progression, or withdrawal from the study • The final analyses were planned to be carried out after all patients had completed or discontinued the study due to any reason. No formal hypothesis testing was performed at the final analysis However, as data from at least 75 patients treated with liso-cel who had at least six months follow-up for DoR were required for registration, the planned interim analysis was not performed. The primary analysis for the DLBCL Cohort was planned after at least 75 patients in the primary analysis set in a dose confirmation group had been treated, and these patients had been followed for at least 6 months or until death, disease progression, or withdrawal from study. The target number of patients was achieved as of the 12th April 2019 DCO, with a median on-study follow-up of nine months. At this time, the primary analysis set included 133 patients with DLBCL NOS (de novo or transformed from FL), or HGL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology.
Sample size, power calculation	• For the primary analysis of ORR, a sample size of 75 patients in the primary analysis set would provide approximately 98% power to demonstrate statistical significance at a one-sided significance level of 0.021 based on an exact test • For the primary analysis of CR rate, a sample size of 75 patients in the primary analysis set would provide approximately 96% power to demonstrate statistical significance at a one-sided significance level of 0.021 based on an exact test

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	• For the primary analysis of ORR for chemorefractory patients based on the primary analysis set, 45 chemorefractory patients would provide ~89% power to demonstrate statistical significance at a 1-sided significance level of 0.021 based on an exact test • For the primary analysis of CR rate for chemorefractory patients based on the primary analysis set, 45 chemorefractory patients would provide ~90% power to demonstrate statistical significance at a 1-sided significance level of 0.021 based on an exact test
Data management, patient withdrawals	• For OS assessment, data from surviving patients were censored at the last time the patient was known to be alive. Data include all available survival information with LTFU data • According to FDA censoring rules for PFS and DOR, censoring reasons included ongoing, study discontinuation or completion, receipt of another anticancer treatment (including retreatment with liso-cel), receipt of transplant and ≥2 consecutive missed scheduled disease assessments. According to these rules, patients were censored at the date of the last adequate disease assessment on or prior to the earliest censoring event • According to EMA censoring rules for PFS and DOR, censoring is not performed for patients who begin a new anticancer therapy, receive a transplant or have ≥2 consecutive missed scheduled disease assessment. According to these rules, patients were censored at the date of the last adequate disease assessment on or prior to the earliest censoring event PFS and ORR from the 28th September 2021 DCO were presented according to both EMA and FDA censoring rules.[132, 133] Within this submission, the results using the EMA censoring rules have been presented. The results according to FDA censoring rules are available within the CSR submitted alongside the submission.[120]
Multiplicity	In the primary analysis, the hypotheses were tested in a sequential order for endpoints: 1) ORR; 2) CR; 3) ORR for chemorefractory subjects; 4) CR for chemorefractory subjects. Hypothesis testing of an endpoint was performed only if the null hypothesis of the preceding endpoint was rejected. The group sequential method and sequential testing procedure will preserve the overall 1-sided type I error at 0.025. The hypothesis testing and sequential testing procedure of the interim analysis was planned to be the same as the primary analysis.

Abbreviations: BCL2/6: B-cell lymphoma gene 2/6; CR: complete response; CSR: clinical study report; DCO: data cut-off; DLBCL: diffuse large b-cell lymphoma; DoR: duration of response; EMA: European Medicines Agency; FDA: Food and Drugs Administration; FL: follicular lymphoma; HGL: High-grade lymphoma; LTFU: long-term follow-up; MYC: myelocytomatosis oncogene; NOS: not otherwise specified; ORR: objective response rate; PFS: progression-free survival.
Source: BMS Data on File. TRANSCEND Statistical Analysis Plan.[131]

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B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

TRANSCEND was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), it is considered to be a good-quality study. The quality assessment of the TRANSCEND trial has been conducted using the Downs and Black checklist, which is recommended for use with non-RCTs (Table 15).[134] The overall risk of bias in the TRANSCEND trial was considered to be low. Full details of the clinical SLR, including methods and results of the quality assessment can be found in Appendix D.

Table 15: Assessment of quality and risk of bias in the TRANSCEND trial

Question	TRANSCEND
Reporting	
Is the hypothesis/aim/objective of the study clearly described?	Yes
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes
Are the interventions of interest clearly described?	Yes
Are the distributions of principal confounders in each group of patients to be compared clearly described?	N/A
Are the main findings of the study clearly described?	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	No
Have all important adverse events that may be a consequence of the intervention been reported?	Yes
Have the characteristics of patients lost to follow-up been described?	No
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N/A
External validity	
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	Yes
Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes
Internal validity - bias	
Was an attempt made to blind study patients to the intervention they received?	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	No
If any of the results of the study were based on 'data dredging', was this made clear?	N/A
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes

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Question	TRANSCEND
Were the statistical tests used to assess the main outcomes appropriate?	Yes
Was compliance with the intervention(s) reliable?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Internal validity - confounding (selection bias)	
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A
Were study patients randomised to intervention groups?	N/A
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N/A Primary outcome of ORR was based on IRC assessments to minimise bias
Were losses of patients to follow-up taken into account?	Yes
Power	
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N/A Power was sufficient to detect a clinically meaningful response

Abbreviations: IRC: independent review committee; N/A: not applicable; ORR: objective response rate.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 TRANSCEND

B.3.6.1.1 Summary of key efficacy outcomes

A summary of the primary and key secondary efficacy endpoints from the final analysis of the DLBCL Cohort Efficacy Set (N=216) is presented in Table 16. For each endpoint, results are presented for the DL1+DL2 dosing regimens, aligned with the marketing authorisation for liso-cel in this indication (see Section B.3.3.1, Table 7).[1] All efficacy endpoints have been presented from the most recent DCO from which they are available (28th September 2021) except for OS, which includes long-term follow-up data from GC-LFTU-001 (DCO: 31st January 2024). At the September 2021 DCO, the median on-study follow-up of the DLBCL Cohort Efficacy Set was [redacted] months (range: [redacted]).[125]

Treatment with liso-cel resulted in a rapid, high rate of durable CR among patients with R/R LBCL. The durable treatment benefit of liso-cel has the potential to prolong survival amongst patients, whilst maintaining a manageable safety profile (see Sections B.3.6.1.3 and B.3.10.1, respectively). Additionally, treatment with liso-cel was shown to drive improvements in HRQoL, with clinically meaningful improvements reported by patients (Section B.3.6.1.3).

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Table 16: Summary of key clinical results from the TRANSCEND trial (DLBCL Cohort Efficacy Set)

Outcome	DCO	DL1+DL2 (N=216)
ORR (CR + PR), % (95% CI)[a]	28th September 2021	72.7 (66.2, 78.5)
Median DoR, months (95% CI)[b, c]	28th September 2021	20.5 (8.2, NR)
Median PFS (assessed by IRC), months (95% CI)[b]	28th September 2021	[redacted]
Median OS, months (95% CI)[b, d]	31st January 2024	[redacted]
Change in EORTC QLQ-C30 global health status from baseline to post dose Month 24, mean (SD)	31st January 2024	[redacted] ([redacted])
Change from baseline in EQ-5D-5L index score at post dose Month 24, mean (SD)	31st January 2024	[redacted]

Footnotes: [a] 2-sided 95% exact Clopper-Pearson CIs. [b] KM method is used to obtain 2-sided 95% CIs. [c]Patients with CR or PR. [d] Survival data combines OS data from the 28th September 2021 DCO of TRANSCEND with additional LTFU data from the 31st January 2024 DCO of GC-LTFU-001.
Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; EQ-5D-5L: five-level EQ-5D; IRC: Independent Review Committee; EORTC: European Organisation for Research and Treatment of Cancer; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; QLQ-C30: quality of life questionnaire core-30; SD: standard deviation.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021);[120] BMS Data on File (TRANSCEND Clinical Study Report, May 2024);[59] Liso-cel SmPC.[1]

B.3.6.1.2 Primary endpoint: Overall response rate

At the primary analysis (12th April 2019 DCO), the study had met its primary and key secondary endpoints (ORR and CR rate per IRC assessment) in the primary analysis set, after a median follow-up of [redacted] months (N=[redacted]; ORR: [redacted]% [95% CI: [redacted]]; CR rate: [redacted]% [95% CI: [redacted]]).[126] The final analysis (28th September 2021 DCO) provided longer-term follow-up data for the DLBCL Cohort Efficacy Set and had similar response rates to those reported at the primary analysis.[120] An overview of response rate outcomes is presented in Table 17. The majority of patients experienced a response to liso-cel, with an ORR observed in 157 (72.7%) patients. Of these patients, 115 (53.2%) achieved CR, demonstrating the high proportion of patients expected to achieve a deep response with liso-cel treatment.[1, 120]

A sensitivity analysis was conducted for ORR by investigator assessment was performed, the results of which were consistent with the main analysis. Details of the sensitivity analysis can be found in Appendix J. The ORR results for the subgroup analyses were generally consistent with those in the overall population (Section B.3.7). The capacity of liso-cel to deliver a measurable and meaningful tumour response across subgroups underscores its potential as an effective treatment option in patients with R/R DLBCL (Section B.3.7).

Table 17: ORR per IRC Assessment (DLBCL Cohort Efficacy Set; 28th September 2021 DCO)

	DL1+DL2 (N=216)
BOR, n (%)[a]	
CR	115 (53.2)
PR	42 (19.4)
SD	[redacted]

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	DL1+DL2 (N=216)
Non-PD	[redacted]
PD	[redacted]
NE	[redacted]
ORR	
CR + PR, n (%)	157 (72.7)
95% CI[b]	66.2, 78.5
CR	
CR, n (%)	115 (53.2)
95% CI[b]	46.4, 60.0

Footnotes: [a]BOR is the best disease response recorded from the time of the final liso-cel infusion of the initial cycle until disease progression, EOS, the start of another anticancer therapy, or HSCT. [b]2-sided 95% exact Clopper-Pearson CIs.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; EOS: end of study; HSCT: hematopoietic stem cell transplant; IRC: Independent Review Committee; NE: not evaluable; ORR: overall response rate; PD: progressed disease; PR: partial response; SD: stable disease.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 7.2-1);[120] Liso-cel SmPC.[1]

B.3.6.1.3 Secondary endpoints

Duration of response

Results for DoR by IRC assessment, following EMA censoring rules (Table 14), DLBCL Cohort Efficacy Set are presented in Table 18 and the KM curve is presented in Figure 6. Further details of the analysis of DoR by BOR is presented in Appendix J.

With a median follow-up of [redacted] months, the median DOR per IRC assessment was 20.5 months (95% CI: 8.2, NR), with [redacted]% (95% CI: [redacted] of patients continuing to respond to treatment at 24 months, demonstrating the durable benefit of liso-cel.[1, 120] Treatment with liso-cel was associated with a rapid response and a sustained benefit.

Table 18: DoR per IRC assessment, EMA censoring rules (DLBCL Cohort Efficacy Set; 28th September 2021 DCO)

	DL1+DL2 (N=216)
Patients with CR or PR	**157 (72.7)**
Patients with PR	42 (19.4)
Patients with CR	115 (53.2)
Duration of response, months	
Median (95% CI)	20.5 (8.2, NR)
Progression or Death, n (%)	[redacted]
Progression	[redacted]
Death	[redacted]
Censored, n (%)	[redacted]
Ongoing	[redacted]
Completed the study	[redacted]

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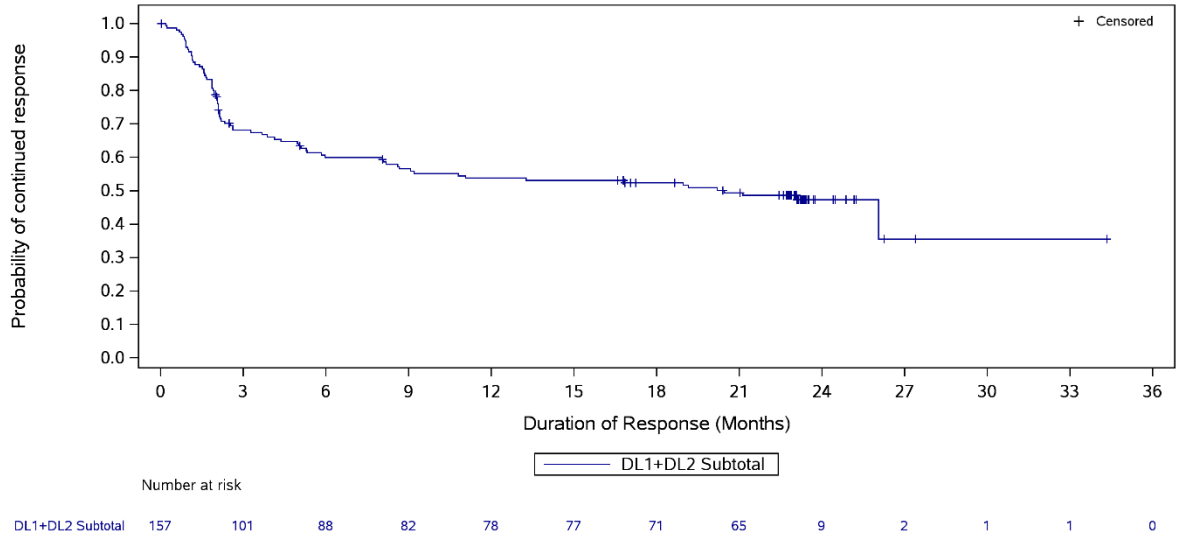
	DL1+DL2 (N=216)
Discontinued the study	[redacted]
Received liso-cel retreatment	[redacted]
Probability of continued repose post-initial response, % (95% CI)	
≥6 months	[redacted]
≥12 months	[redacted]
≥18 months	[redacted]
≥24 months	[redacted]

Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; EMA: European Medicines Agency; IRC: Independent Review Committee; PR: partial response.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 7.3.2 and Table 7.3.2-2);[120] Liso-cel SmPC.[1]

Figure 6: DoR by IRC assessment, EMA censoring rules (DLBCL Cohort Efficacy Set; 28th September 2021 DCO)



Abbreviations: CR: complete response; DCO: data cut-off; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; FDA: Food and Drug Administration; IRC: Independent Review Committee; PR: partial response.
Source: BMS Data on File; Liso-cel SmPC.[1]

The median time to first response (i.e. first CR or PR) per IRC assessment was [redacted] months (95% CI: [redacted]) (Table 19).

Table 19: Time to response per IRC assessment (DLBCL Cohort Efficacy Set, 28th September 2021 DCO)

	DL1+DL2 (N=[redacted])
Time to first CR or PR, months	
n (%)	[redacted]
Median (range)	[redacted]
Time to first CR, months	
n (%)	[redacted]

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	DL1+DL2 (N=[redacted])
Median (range)	[redacted]

Abbreviations: CR: complete response; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; IRC: Independent Review Committee; PR: partial response.
Source: BMS Data on File (TRANSCEND Clinical Study Report, 2024 – Table 14.2.3.2.a)[59]

Progression-free survival

PFS by IRC assessment, following EMA censoring rules, is presented in Table 20. PFS by BOR (CR or PR) are presented in Appendix J..4. After a median follow-up of [redacted] months, the median PFS per IRC assessment was [redacted] months (95% CI: [redacted]). The plateau of the KM curve between 6 and 12 months suggests the potential for long-term remission, with few patients experiencing progression if they remained progression free during this initial period (Figure 7). This is supported by the fact that [redacted]% of patients (95% CI: [redacted]) remained progression-free at 24 months.[120] These results reflect the value of CAR T-cell therapies in maintaining disease control over a prolonged period and providing a curable treatment option for R/R DLBCL, PMBCL and FL3B.

A sensitivity analysis for investigator assessed PFS in the DLBCL Cohort Efficacy Set was performed, the results of which were consistent with the main analysis (Appendix J).

Table 20: PFS per IRC assessment, EMA censoring rules (DLBCL Cohort Efficacy Set; 28th September 2021 DCO)

	DL1+DL2 (N=216)
PFS, months	
Median (95% CI)	[redacted]
PFS events, n (%)	[redacted]
Progression	[redacted]
Death	[redacted]
Censored, n (%)	[redacted]
Ongoing	[redacted]
Completed the study	[redacted]
Discontinued the study	[redacted]
Received liso-cel retreatment	[redacted]
Probability of PFS, % (95% CI)	
≥6 months	[redacted]
≥12 months	[redacted]
≥18 months	[redacted]
≥24 months	[redacted]

Abbreviations: CI: confidence interval; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; EMA: European Medicines Agency; IRC: Independent Review Committee; PFS: progression-free survival.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 7.3.3-1)[120]

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Figure 7: PFS by IRC assessment, EMA censoring rules (DLBCL Cohort Efficacy Set; 28th September 2021 DCO)

Abbreviations: CR: complete response; DCO: data cut-off; DLBCL: diffuse large B-cell lymphoma; EMA: European Medicines Agency; IRC: Independent Review Committee; PFS: progression-free survival; PR: partial response.
Source: BMS Data on File.

Overall survival

The OS analysis included all available survival data from TRANSCEND (DCO: 28th September 2021), in addition to LTFU data from the GC-LTFU-001 study (31st January 2024 DCO). Of the [redacted] patients, [redacted] ([redacted]%) consented to being part of the LTFU study.[59] OS data are presented in Table 21 and the associated KM curve is presented in Figure 8.

After a median follow-up of [redacted] months, the median OS for patients receiving liso-cel was [redacted] months (95% CI: [redacted]). There were [redacted] deaths ([redacted]%) out of the [redacted] patients. After seven years, over [redacted]% of patients remained alive, demonstrating the potential for liso-cel to improve long-term survival in patients.[59] The OS KM curve demonstrates a more steady decline in survival rate and improved prognosis after ~18 months since treatment with liso-cel.

Table 21: OS (DLBCL Cohort Efficacy Set; GC-LTFU-001 31st January 2024 DCO)

	DL1+DL2 (N=216)
Events, n (%)	
Death	[redacted]
OS, months	
Median (95% CI)	[redacted]
Probability of OS, % (95% CI)	
≥6 months	[redacted]
≥12 months	[redacted]
≥18 months	[redacted]
≥24 months	[redacted]
≥30 months	[redacted]
≥36 months	[redacted]

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	DL1+DL2 (N=216)
≥42 months	[redacted]
≥48 months	[redacted]
≥54 months	[redacted]
≥60 months	[redacted]
≥72 months	[redacted]
≥84 months	[redacted]

Abbreviations: CI: confidence interval; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; OS: overall survival.
Source: BMS Data on File (TRANSCEND Clinical Study Report, May 2024 – Table 8).[59]

Figure 8: OS by IRC assessment (DLBCL Cohort Efficacy Set, GC-LTFU-001 31st January 2024 DCO)

Abbreviations: CR: complete response; DCO: data cut-off; DLBCL: diffuse large B-cell lymphoma; IRC: Independent Review Committee; OS: overall survival; PR: partial response.
Source: BMS Data on File.

HRQoL

Measurement of HRQoL changes were assessed using EORTC QLQ-C30 and the EQ-5D-5L. A notable proportion of patients treated with liso-cel demonstrated clinically meaningful improvements in HRQoL at various timepoints across all pre-specified domains of EORTC QLQ-C30 and EQ-5D-5L.[59]

EORTC QLQ-C30

[redacted] patients were evaluable for the EORTC QLQ-C30 questionnaire. Compliance rates were [redacted]%, [redacted]% and [redacted]%, at 9, 18 and 24 months (Appendix J). Compared to baseline, mean scores in GHS showed improvement from Months 1 to 24 (Table 22), demonstrating a clinically meaningful improvement for patients over time. The mean change in EORTC QLQ-C30 global health status from baseline to post dose Month 24 was [redacted] (SD: [redacted]).[59]

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Table 22: Change from baseline for EORTC QLQ-C30 (DLBCL Cohort Treated Set; 31st January 2024 DCO)

Post Dose	DL1+DL2 (N=[redacted])
Change from baseline GHS, mean (SD)	
Day 29	[redacted]
Month 2	[redacted]
Month 3	[redacted]
Month 6	[redacted]
Month 9	[redacted]
Month 12	[redacted]
Month 18	[redacted]
Month 24	[redacted]

Abbreviations: DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; EORTC QLQ-C30: European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS: global health status; SD: standard deviation.
Source: BMS Data on File (TRANSCEND Clinical Study Report, May 2024 – Table 14.2.8.4.2)[59]

EORTC QLQ-C30 scores for physical functioning, pain and fatigue are presented in Appendix J. The mean change in EORTC QLQ-C30 physical functioning, pain and fatigue from baseline to post dose Month 24 was [redacted] (SD: [redacted]), [redacted] (SD: [redacted]) and [redacted] (SD: [redacted]), respectively.[59]

EQ-5D-5L

[redacted] patients were evaluable for the EQ-5D-5L questionnaire, having completed both the EQ-5D-5L health utility index and EQ-VAS at baseline and at least one post liso-cel infusion.[59, 135] Compliance rates were [redacted]%, [redacted]% and [redacted]%, at 9, 18 and [redacted] months (Appendix J).[59]

Mean change in baseline EQ-5D-5L scores decreased one month after liso-cel infusion, most likely due to the transient toxicity associated with liso-cel infusion (Table 23). This was followed by fluctuations in scores between Months 2 and 3 and improvements from Months 6 to [redacted]. The mean change from baseline EQ-5D-5L index score at post dose Month 24 was [redacted]).[59] EQ-VAS scores are provided in Appendix J.

Table 23: Change from baseline for US based EQ-5D-5L index scores (DLBCL Cohort Treated Set; 31st January 2024 DCO)

Post Dose, mean (SD)	DL1+DL2 (N=[redacted])
Day 29	[redacted]
Month 2	[redacted]
Month 3	[redacted]
Month 6	[redacted]
Month 9	[redacted]
Month 12	[redacted]
Month 18	[redacted]
Month 24	[redacted]

Abbreviations: DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; EQ-5D-5L: five-level EQ-5D; SD: standard deviation; US: United States.
Source: BMS Data on File (TRANSCEND Clinical Study Report, May 2024 – Table 14.2.9.4.1)[59]

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B.3.6.2 GC-LTFU-001

The full details of the trial methodology for GC-LTFU are presented in Appendix M. Long-term survival data from the GC-LTFU-001 study are captured in the OS results from the TRANSCEND and TRANSCENDWORLD, presented in Section B.3.6.1.3 and B.3.6.3.

B.3.6.3 TRANSCENDWORLD

In addition to TRANSCEND trial, supportive clinical data for the efficacy and safety of liso-cel in an international population are provided by TRANSCENDWORLD (see Section B.3.2, Table 6). A summary of the primary and key secondary efficacy endpoints from the TRANSCENDWORLD trial are presented in Table 24. Full details of the TRANSCENDWORLD methodology are presented in Appendix K. Baseline characteristics of patients in TRANSCENDWORLD were comparable to those reported for patients in TRANSCEND (see Section B.3.3.6 and Appendix K.1).[120, 125] Patients must have had PET-positive disease as per Lugano Classification. The data set used for the analyses of efficacy and safety in TRANSCENDWORLD is the Liso-cel Treated Set, defined as all patients who received liso-cel conforming product in accordance with drug product release specifications, in line with the DLBCL Cohort Efficacy Set in the TRANSCEND trial. Patients in the TRANSCENDWORLD trial received liso-cel at DL2S (100×10^6 CAR+ T cells [50×10^6 CD8+ CAR+ T cells and 50×10^6 CD4+ CAR+ T cells]).

The study trial met its primary and key secondary endpoints for Cohort 1. All efficacy endpoints have been presented from the most recent DCO from which they are available (28th October 2021) except for OS, which includes long-term follow-up data from GC-LFTU-001 (DCO: 31st January 2024; see Section B.3.3.5, Table 12). For each endpoint, results are presented for Cohort 1, as this is the only cohort relevant to the decision problem in this submission (see Section B.3.2, Table 6). Generally, efficacy results were comparable to those presented in TRANSCEND. At the 28th October 2021 DCO, the median duration of follow-up after liso-cel infusion was 15.8 months (range: [redacted]) for Cohort 1.[1, 125]

Table 24: Summary of key clinical results (TRANSCENDWORLD; Cohort 1, Liso-cel Treated Set)

Outcome	DCO	Cohort 1 (N=36)
ORR (CR + PR), % (95% CI)[a]	28th October 2021	61.1 (43.5, 76.9)
Median DoR (assessed by IRC), months (95% CI)[a]	28th October 2021	[redacted]
Median PFS (assessed by IRC), months (95% CI)[a]	28th October 2021	[redacted]
Median EFS (assessed by IRC), months (95% CI)[a]	28th October 2021	[redacted]
Median OS, months (95% CI)[a, b]	31st January 2024	[redacted]

Footnotes: [a] Median is estimated from Kaplan-Meier product-limit estimates. [b] Includes survival data from the January 2024 LTFU study GC-LTFU-001.[121]
Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; DoR: duration of response; EFS: event-free survival; IRC: Independent Review Committee; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response.
Source: BMS Data on File (TRANSCENDWORLD Clinical Study Report Addendum 01, 2021);[125] Liso-cel SmPC.[1]

B.3.6.4 OUTREACH

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Supportive data for the use of liso-cel in an outpatient setting are provided by the OUTREACH trial.[110] A summary of the key efficacy endpoints are provided in Table 25, with all efficacy endpoints have been presented from the June 2022 DCO. Full details of the OUTREACH methodology are presented in Appendix L.

At the June 2022 DCO, the median follow-up was 10.6 months (range: 1.0, 24.5). Liso-cel demonstrated meaningful efficacy with favourable safety in patients with R/R LBCL; however, OS data for the outpatient population remains immature. Similar ORR was observed for both the outpatient and inpatient study arms, demonstrating a measurable and meaningful tumour response with liso-cel regardless of treatment setting.[110] Further efficacy endpoints are presented in Appendix L.

Table 25: Summary of efficacy endpoints (OUTREACH; Liso-cel Treated Set; June 2022 DCO)

Outcome	Outpatients (N=57)	Inpatients (N=25)
Median PFS (assessed by IRC), months (95% CI)[a]	6.05 (2.9, NR)	4.3 (2.8, NR)
Median OS, months (95% CI)[a]	NR (9.2, NR)	22.2 (8.0, NR)
ORR (CR + PR), % (95% CI)[a]	82 (70.1, 91.3)	76 (54.9, 90.6)
Median DoR, months (95% CI)[a]	11.1 (3.9, NR)	NR (2.1, NR)

Footnotes: [a] Kaplan-Meier method is used to obtain 2-sided 95% CIs.
Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; DoR: duration of response; IRC: independent review committee; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival: PR: partial response.
Source: Linhares et al. (2024).[110]

B.3.7 Subgroup analysis

In TRANSCEND, pre-specified subgroup analyses were conducted for ORR and CR rate as per IRC assessment, based on the following factors:[125]

- Age (<40, ≥40 to <65, and ≥65 years; <65 versus ≥65 years; <75 versus ≥75 years)
- Sex (male versus female)
- Ethnicity (Hispanic or Latino versus not Hispanic or Latino)
- Race (White versus other races)
- Prior haematopoietic stem cell transplantation status (yes versus no)
- Prior response status (refractory versus relapsed to last prior therapy)
- Prior chemotherapy response status (chemorefractory versus chemosensitive to last prior chemotherapy-containing therapy)
- CNS disease status (known CNS disease versus no known CNS disease at the time of the first liso-cel infusion)
- DLBCL cell of origin (germinal centre B-like versus non-germinal centre B-like)

Across all subgroups, the ORR results were generally consistent with those in the overall population with overlapping 95% CIs and the differences between subgroups were not considered to be clinically meaningful (Figure 9). Liso-cel demonstrated clinically meaningful activity across all patient subgroups, including patients with high-risk features, such as high-grade B-cell lymphoma, those aged 65 years or older, and patients with chemotherapy-refractory disease. Durable responses (ORR by IRC) were seen across B-cell lymphoma subtypes.

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Figure 9: Forest plot of ORR by IRC assessment (DLBCL Cohort Efficacy Set; DCO: 21st September 2021)

Footnotes: ORR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed. Right-hand side dotted vertical line corresponds to the ORR (72.8%) in the DLBCL Efficacy Set. Left-hand side dotted vertical line corresponds to the null hypothesis of ORR ≤40%.
Abbreviations: ABC: activated B-cell; CI: confidence interval; CNS: central nervous system; DCO: data cut-off; DLBCL: diffuse large B-cell lymphoma; FL3B: follicular lymphoma grade 3B; GCB: germinal centre b-cell; HGL: high-grade lymphoma; HSCT: hematopoietic stem cell transplantation; iNHL: indolent non-hodgkin lymphoma; N: number; NOS: not otherwise specified; ORR: objective response rate; PMBCL: primary mediastinal B-cell lymphoma; tFL: transforming follicular lymphoma.
Source: BMS Data on File.

B.3.8 Meta-analysis

No relevant meta-analyses were conducted.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Identification of comparator studies

As described in Section B.3.1, an SLR was conducted to identify relevant published data for the management of LBCL at 3L+. Full details of the methodology and results of this SLR are presented in Appendix D. Across the entire database search covering the period from 2003 to September 2025, a total of 191 eligible publications reporting on 13 unique studies were included in the clinical SLR. Of these, no head-to-head RCTs between liso-cel and axi-cel were identified. As such, a MAIC was conducted to assess the relative efficacy and safety of liso-cel compared with axi-cel in adults with R/R LBCL at 3L+. The PRISMA diagram is presented in Appendix D.2

The SLR identified the ZUMA-1 trial as key source of efficacy and safety data for axi-cel as a 3L+ treatment option for patients with R/R LBCL.[136]

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B.3.9.2 Studies of interest

The ZUMA-1 trial was a Phase 1-2, single-arm, multicentre, open-label, registrational trial that investigated the efficacy and safety of axi-cel in patients with R/R DLBCL, PMBCL or transformed FL. As the TRANSCEND trial was a single arm trial, an anchored MAIC could not be considered and, as such, an unanchored MAIC was conducted.

Data sources

A MAIC was previously conducted and published in a paper from Maloney *et al.* 2021, estimating the comparative efficacy and safety of liso-cel from the TRANSCEND study (DCO: August 2019) relative to axi-cel using data from the ZUMA-1 study (DCO: August 2018) for patients with LBCL at 3L+.[137] The efficacy outcomes considered were PFS, OS, ORR and CR. The data used for liso-cel was based on the full trial population, including all dose levels (DL1, DL2 and DL3; see Table 7). Since the original published MAIC, updated DCOs for both the ZUMA-1 (DCO: 11th August 2021) and TRANSCEND (DCO: 28th September 2021 [PFS, ORR and CR]; DCO: 31st January 2024 [OS]) trials have been collected, providing longer-term OS and PFS data. In addition, updated data on Grade ≥3 infections are available for liso-cel. To address these changes, the MAIC was updated, incorporating the latest available data from each study. In addition, the data used for liso-cel was informed by the DL1+DL2 subtotal of the DLBCL Cohort from TRANSCEND, to align with the MHRA approved dosing regimens for liso-cel.

The primary sources of data for axi-cel used to inform the updated MAIC were the peer-reviewed publications for ZUMA-1 (Table 26). Secondary data sources for ZUMA-1 from the same DCO were used for any information not available in the primary publications or when additional clarity was required, with preference placed on European regulatory documents where available. For liso-cel, the primary data source used to inform the updated MAIC was IPD from the TRANSCEND trial.

Table 26: Data Sources for the ZUMA-1 Trial

Information Obtained	ZUMA-1 Trial Data Sources (Axi-cel)
Trial Design and Eligibilities	Locke (2019)[138]
Baseline Patient Characteristics	Locke (2019)[138] Yescarta [EMA EPAR] [139]
Efficacy Outcomes	Locke (2019)[138] Neelapu (2023)[109] Yescarta [EMA SmPC][140]
Safety Outcomes	Locke (2019)[138] Yescarta[a] [BLA Clinical Review Memorandum][141] Yescarta [EMA SmPC][140]

Abbreviations: Axi-cel: axicabtagene ciloleucel; BLA: biologics licence application; EMA: European Medicines Agency; EPAR: European Public Assessment Report; SmPC: Summary of Product Characteristics.
Footnotes: [a]Source for NEs per ND/PD SOC definition.
Source: BMS Data on File (MAIC Report 2025; Table 1).[136]

A summary of efficacy and safety outcomes for the patient cohorts in each trial is presented in Table 27. For all efficacy outcomes, data for liso-cel were informed by the DL1+DL2 subgroup of the DLBCL Cohort Efficacy Set Efficacy Set (N=216) from TRANSCEND at the most recent DCO available, in line with the data presented in Section B.3.6. OS data are informed by the 31st January 2024 DCO, with all other efficacy outcomes informed by the 28th September 2021 DCO. For axi-cel, efficacy outcomes were informed by the Phase 2 modified intention-to-treat (mITT) Set (N=101) from the ZUMA-1 trial (11th August 2021 DCO).

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For all safety outcomes, the DL1+DL2 subgroup of the TRANSCEND DLBCL Cohort Treated Set (N=229) was used for liso-cel (DCO: 28th September 2021) and the ZUMA-1 Phase 1+2 Safety Analysis Set was used for axi-cel (N=108; DCO: 11th August 2018).

Table 27: Summary of datasets used in the updated MAIC for liso-cel and axi-cel

Treatment	Trial Name	DCO[a]	Median Follow-up, months	Analysis Set	N
Efficacy Outcomes					
Liso-cel (OS)	TRANSCEND plus GC-LTFU-001	31st January 2024	[redacted]	DLBCL Cohort Efficacy Set (DL1+DL2)	216
Liso-cel (PFS)	TRANSCEND	28th September 2021	[redacted]	DLBCL Cohort Efficacy Set (DL1+DL2)	216
Axi-cel (PFS, OS)	ZUMA-1	11th Aug 2021	63.1	Phase 2 mITT Set	101
Safety Outcomes					
Liso-cel	TRANSCEND	28th September 2021	[redacted]	DLBCL Cohort Treated Set (DL1+DL2)	229
Axi-cel	ZUMA-1	11th Aug 2018	27.4[b]	Phase 1+2 Safety Analysis Set	108

Abbreviations: Axi-cel: axicabtagene ciloleucel; CAR: chimeric antigen receptor; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; IQR: interquartile range; Liso-cel: lisocabtagene maraleucel; MAIC: matching-adjusted indirect comparison; mITT: modified intention-to-treat; N: number; N/A; not applicable; OS: overall survival; PFS: progression-free survival.
[a] DCOs with the most complete data availability were included. [b] The way in which median follow-up time was calculated was not reported (Locke, 2019[138], Yescarta [Summary of Product Characteristics]).[140] Median on-study follow-up time was reported, which is defined as (EOS date – first dose date + 1)/30.4375. If patients were continuing on study, the data cutoff date was used to impute the EOS date for the purpose of the calculation.
Source: BMS Data on File (MAIC Report 2025; Table 2);[136] BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, 2021).[120]

As discussed in Section B.2.1, PFS and OS typically represent the key endpoints used in economic models in this indication, in alignment with the key outcomes included in the cost-effectiveness model in NICE TA872 (Table 4).[6] As such, this section reports MAIC results on PFS and OS as the key efficacy outcomes, alongside safety outcomes. MAIC results for ORR and CRR are presented within the MAIC report included within the reference pack accompanying this submission.[136]

B.3.9.3 Feasibility assessment

A feasibility assessment was performed to assess heterogeneity across TRANSCEND and ZUMA-1.[120, 138]

Study design

The trial designs were broadly comparable:

- Both studies were multicentre, open-label, single-arm trials
- In both trials, patients received similar LDC, namely fludarabine and cyclophosphamide

However, some differences were identified:

- Bridging therapy was permitted in TRANSCEND, whereas in ZUMA-1 patients were not permitted to receive bridging therapies

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- TRANSCEND was conducted in the US only, whereas ZUMA-1 had enrolment sites globally
- CAR T-cell dosage varied across trials

A summary of the key trial design features in both trials is presented in Table 28, with further details presented in Table 6, Appendix D.2.3.

Table 28: Comparison of Trial Design Features between TRANSCEND and ZUMA-1

Key Trial Design Features	TRANSCEND (Liso-cel)	ZUMA-1 (Axi-cel)
Phase	1	1 and 2
Design	Single arm	Single arm
Blinding	Open label	Open label
Centres	Multicentre	Multicentre
Country	US	Multiple (US, Canada, France, Germany, Israel and Netherlands)
Bridging Therapy	Allowed	Not allowed
PET-positive Disease after Bridging Therapy	Confirmed	Not applicable
Lymphodepleting Chemotherapy	Yes	Yes
Regimen and Dosage of Lymphodepleting Chemotherapy	Fludarabine (30 mg/m^2/day for 3 days) and cyclophosphamide (300 mg/m^2/day for 3 days), completed 2-7 days before infusion	Fludarabine (30 mg/m^2) and cyclophosphamide (500 mg/m^2) on the fifth, fourth, and third day before infusion
CAR T-cell Regimen and Dosage	• **DL1S:** 50 × 10^6 CAR+ T cells (25 × 10^6 CD8+ CAR+ T cells and 25 × 10^6 CD4+ CAR+ T cells) • **DL1D:** 50 × 10^6 CAR+ T cells • **DL2:** 100 × 10^6 CAR+ T cells (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells) • **DL3:**[a] 150 × 10^6 CAR+ T cells (75 × 10^6 CD8+ CAR+ T cells and 75 × 10^6 CD4+ CAR+ T cells)	Single infused dose of 2 × 10^6 CAR+ T cells per kg of bodyweight, with a maximum permitted dose of 2 × 10^8 CAR T cells

Abbreviations: Axi-cel: axicabtagene ciloleucel; CAR: Chimeric antigen receptor; IV: intravenous; Liso-cel: lisocabtagene maraleucel; PET: positron emission tomography; US: United States.
Footnotes: [a] DL3, single-dose regimen: 150 × 10^6 CAR+ T cells (75 × 10^6 CD8+ CAR+ T cells and 75 × 106 CD4+ CAR+ T cells) was included in TRANSCEND but is not an authorised dose of liso-cel and, therefore, has not been considered within the MAIC.
Source: BMS Data on File (MAIC Report 2025; Table 3).[136]

Population

Comparison of eligibility criteria across the trials revealed that trials had sufficient overlap in patient populations to conduct a MAIC (Table 29).

TRANSCEND enrolled a broader patient population than the ZUMA-1 trials in terms of permitted NHL subtypes, ECOG PS, treatment history, and comorbidities. Notably, only TRANSCEND enrolled patients with FL3B, per eligibility criteria. The ZUMA-1 trial enrolled patients with ECOG PS of 0 and 1, whereas TRANSCEND also enrolled patients with an ECOG PS of 2. TRANSCEND was the only

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trial that permitted patients with previous allo-HSCT; secondary CNS involvement; more impaired renal function, defined as creatine clearance (CrCl) <60 mL/min/1.73 m^2 and >30 mL/min/1.73 m^2, more impaired cardiac function, defined as left ventricular ejection fraction (LVEF) <45% and ≥40%; and had no minimum hematologic parameter requirement.

Table 29: Comparison of Eligibility Criteria between TRANSCEND and ZUMA-1

Eligibility Criteria	TRANSCEND (Liso-cel)	ZUMA-1 (Axi-cel)
Key Inclusion Criteria		
NHL Subtypes	DLBCL NOS, HGL, tFL, PMBCL, tiNHL, FL3B	DLBCL NOS, HGL, tFL, PMBCL, tiNHL[a]
Age	≥18 years	≥18 years
ECOG PS	≤2[b]	≤1
Prior Lines of Treatment	≥2	≥2[c]
Prior Auto-HSCT	Allowed	Allowed, but not within 6 weeks of infusion
Prior Regimen Required	Anthracycline and rituximab (or other CD20-targeted agents)	Anti-CD20 monoclonal antibody unless INV determines that tumor is CD20 negative, and an anthracycline containing chemotherapy regimen
Response to Prior Therapy	R/R disease after at least 2 lines of therapy or after auto-HSCT	No response to first-line therapy (primary refractory disease); Or no response to second or greater lines of therapy; Or refractory post-auto-HSCT (disease progression or relapsed ≤12 months of auto-HSCT)
Absolute Lymphocyte Count	No minimum requirement[b]	≥100/µL
Absolute Neutrophil Count	No minimum requirement[c]	≥1000/µL
Platelet Count	No minimum requirement[d]	≥75,000/µL
Haemoglobin	No minimum requirement	NR
Alanine Aminotransferase	≤5 × ULN	≤2.5 × ULN
Total Bilirubin	<2.0 mg/dL	≤1.5 mg/dL
Serum Creatinine	≤1.5 × ULN	NR
CrCl	>30 mL/min/1.73 m^2 (Cockcroft Gault)	≥60 mL/min (Cockcroft Gault)
Dyspnoea	Grade ≤1 by CTCAE	Not clinically significant
Oxygen Saturation	≥92% on room air	>92% on room air
LVEF	≥40%	≥50%
Key Exclusion Criteria		
Prior Allo-HSCT	Allowed (not within 90 days of leukapheresis)	Not allowed

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Eligibility Criteria	TRANSCEND (Liso-cel)	ZUMA-1 (Axi-cel)
Active CNS Involvement	Secondary CNS involvement allowed	Not allowed
History of Another Primary Malignancy	Not allowed unless another primary malignancy has been in remission for at least 2 years	Not allowed unless disease free for at least 3 years
Infections	Uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment at the time of leukapheresis or liso-cel administration	Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management
Cardiovascular Conditions or Clinically Significant Cardiac Disease	Within 6 months of screening/enrolment	Within 12 months of enrolment

Abbreviations: allo-HSCT: allogeneic hematopoietic stem cell transplantation; auto-HSCT: autologous hematopoietic stem cell transplantation; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; CrCl: creatinine clearance; CTCAE: Common Terminology Criteria for Adverse Events; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; FL3B: follicular lymphoma grade 3B; HGL: high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*; INV: investigator; IV: intravenous; Liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; NR: not reported; PMBCL: Primary mediastinal B-cell lymphoma; R/R: relapsed or refractory; tFL: DLBCL transformed from follicular lymphoma; tiNHL: DLBCL transformed from other indolent non-Hodgkin lymphoma; ULN: upper limit of normal.
Footnotes: [a] ZUMA-1 histology was classified according to WHO 2008 classification. tiNHL was included under DLBCL NOS histology per WHO 2008 tiNHL was included under DLBCL NOS histology per WHO 2008 and patients with tiNHL were included in ZUMA-1 per study protocol.[138, 142] [b] ECOG PS of 2 was also allowed until Protocol Amendment 5. [c] From ZUMA-1 ClinicalTrials.gov record (NCT02348216). [d] Assessed by the investigator INV to have had adequate bone marrow function to receive lymphodepleting chemotherapy.
Source: BMS Data on File (MAIC Report 2025; Table 4).[136]

Actions were taken to redefine and/or recategorise baseline characteristics to allow for a standardised comparison between trials. A comparison of baseline characteristics between trials demonstrated that key factors were similar between trials for efficacy and safety comparisons. Differences were observed for disease stage, tumour burden, extranodal disease, number of prior lines of therapy, prior auto-HSCT, bridging therapy, and R/R to last therapy when comparing the efficacy datasets. Importantly, these differences contain sufficient overlap, which allows for additional adjustment to align study populations more closely (Table 30).

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Table 30: Comparison of Baseline Characteristics between TRANSCEND (rederived as needed) and ZUMA-1

Baseline Patient Characteristics	Efficacy Comparison		Safety Comparison	
	TRANSCEND (Liso-cel) DLBCL Cohort Efficacy Set, DL1+DL2 (N=216)	ZUMA-1 (Axi-cel) Phase 2 mITT Set (N=101)	TRANSCEND (Liso-cel) DLBCL Cohort Treated Set, DL1+DL2 (N=229)	ZUMA-1 (Axi-cel) Phase 1+2 Safety Analysis Set (N=108)
Age				
Mean (SD)	[redacted]	56.3 (12)	[redacted]	56.0 (12.5)
Sex				
Male, n (%)	[redacted]	68 (67.3)	153 (66.8)	73 (67.6)
IPI Score, per ZUMA-1 Categorisation*, n (%)				
0 to 2	[redacted]	55 (54.5)	[redacted]	60 (55.6)
3 to 4	[redacted]	46 (45.5)	[redacted]	48 (44.4)
5	[redacted]	0	[redacted]	0
Missing	[redacted]	0	[redacted]	0
ECOG PS at Screening, n (%)				
0	[redacted]	42 (41.6)	[redacted]	46 (42.6)
1	[redacted]	59 (58.4)	[redacted]	62 (57.4)
2	[redacted]	0	[redacted]	0
Disease Stage, n (%)				
I or II	[redacted]	15 (14.9)	[redacted]	18 (16.7)
III or IV	[redacted]	86 (85.1)	[redacted]	90 (83.3)
Missing	[redacted]	0	[redacted]	0
Tumour Burden based on Pre-lymphodepleting chemotherapy SPD*, INV-assessed, per ZUMA-1 Definition (cm^2)[a]				

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Baseline Patient Characteristics	Efficacy Comparison		Safety Comparison	
	TRANSCEND (Liso-cel) DLBCL Cohort Efficacy Set, DL1+DL2 (N=216)	ZUMA-1 (Axi-cel) Phase 2 mITT Set (N=101)	TRANSCEND (Liso-cel) DLBCL Cohort Treated Set, DL1+DL2 (N=229)	ZUMA-1 (Axi-cel) Phase 1+2 Safety Analysis Set (N=108)
Mean (SD)	[redacted]	50.4 (43.7)	[redacted]	48.9 (42.8)
Secondary CNS Involvement at Time of Treatment, n (%)				
Yes	[redacted]	0	6 (2.6)	0
No	[redacted]	101 (100)	[redacted]	108 (100)
Extranodal Disease, n (%)				
Yes	[redacted]	70 (69.3)	[redacted]	73 (67.6)
No	[redacted]	31 (30.7)	[redacted]	35 (32.4)
Missing	[redacted]	0	[redacted]	0
Bulky Disease, n (%)				
Yes	[redacted]	17 (16.8)	[redacted]	17 (15.7)
No	[redacted]	84 (83.2)	[redacted]	91 (84.3)
Missing	[redacted]	0	[redacted]	0
Disease Histology*, per ZUMA-1 Categorisation, n (%)				
DLBCL	[redacted]	77 (76.2)	[redacted]	84 (77.8)
tFL	[redacted]	16 (15.8)	[redacted]	16 (14.8)
PMBCL	[redacted]	8 (7.9)	[redacted]	8 (7.4)
FL3B	[redacted]	0	[redacted]	0
Cell of Origin, n (%)				
GCB	[redacted]	NR	[redacted]	52 (48.1)

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Baseline Patient Characteristics	Efficacy Comparison		Safety Comparison	
	TRANSCEND (Liso-cel) DLBCL Cohort Efficacy Set, DL1+DL2 (N=216)	ZUMA-1 (Axi-cel) Phase 2 mITT Set (N=101)	TRANSCEND (Liso-cel) DLBCL Cohort Treated Set, DL1+DL2 (N=229)	ZUMA-1 (Axi-cel) Phase 1+2 Safety Analysis Set (N=108)
ABC Non-GCB	[redacted]	NR	[redacted]	18 (16.7)
Unknown	[redacted]	NR	[redacted]	38 (35.2)
Missing	[redacted]	NR	[redacted]	0
Number of Prior Lines of Therapy*, per ZUMA-1 Definition, n (%)				
1	[redacted]	3 (3.0)	[redacted]	3 (2.8)
2	[redacted]	28 (27.7)	[redacted]	29 (26.9)
3+	[redacted]	70 (69.3)	[redacted]	76 (70.4)
Prior HSCT, n (%)				
Allo-HSCT	[redacted]	0	[redacted]	0
Auto-HSCT	[redacted]	25 (24.8)	[redacted]	29 (26.9)
Bridging Therapy, n (%)				
Yes	[redacted]	0	[redacted]	0
No	[redacted]	101 (100)	[redacted]	108 (100)
R/R to Last Therapy*, per ZUMA-1 Definition, n (%)				
Relapsed	[redacted]	21 (20.8)	[redacted]	25 (23.1)
Refractory	[redacted]	80 (79.2)	[redacted]	83 (76.9)
Missing	[redacted]	0	[redacted]	0
CrCl prior to Lymphodepleting Chemotherapy*, per ZUMA-1 Eligibility Criteria, n (%)				
<60mL/min	[redacted]	0	[redacted]	0

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Baseline Patient Characteristics	Efficacy Comparison		Safety Comparison	
	TRANSCEND (Liso-cel) DLBCL Cohort Efficacy Set, DL1+DL2 (N=216)	ZUMA-1 (Axi-cel) Phase 2 mITT Set (N=101)	TRANSCEND (Liso-cel) DLBCL Cohort Treated Set, DL1+DL2 (N=229)	ZUMA-1 (Axi-cel) Phase 1+2 Safety Analysis Set (N=108)
≥60mL/min	[redacted]	101 (100)	[redacted]	108 (100)
LVEF at Screening*, per ZUMA-1 Eligibility Criteria, n (%)				
<50%	[redacted]	0	[redacted]	0
≥50%	[redacted]	101 (100)	[redacted]	108 (100)
Pre-leukapheresis Absolute Lymphocyte Count (10^9/L)*, per ZUMA-1 Eligibility Criteria, n (%)				
<0.1	[redacted]	0	[redacted]	0
≥0.1	[redacted]	101 (100)	[redacted]	108 (100)
Missing	[redacted]	0	[redacted]	0
Double or Triple Hit, n (%)				
Yes	[redacted]	NR	[redacted]	5 (4.6)
No	[redacted]	NR	[redacted]	42 (38.9)
Unknown	[redacted]	NR	[redacted]	61 (56.5)
History of Any Hematologic Comorbidities[c], n (%)				
Grade ≥3 baseline neutropenia	Assessed for safety comparison only		[redacted]	4 (3.7)
Grade ≥3 baseline thrombocytopenia			[redacted]	4 (3.7)
Grade ≥3 baseline anaemia			[redacted]	3 (2.8)

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Abbreviations: ABC: activated B-cell; ALC: absolute lymphocyte count; Allo-HSCT: allogenic haematopoietic stem cell transplant; Auto-HSCT: autologous haematopoietic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; CrCl: creatinine clearance; CTCAE: common terminology criteria for adverse events; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; FL3B: follicular lymphoma grade 3B; GCB: germinal center B-cell; INV: investigator; IPI: International Prognostic Index; Liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; mITT: modified intention-to-treat; N: number; NR: not reported; PMBCL: Primary mediastinal B-cell lymphoma; R/R: relapsed or refractory; SD: standard deviation; SPD: sum of product of perpendicular diameters; tFL: DLBCL transformed from follicular lymphoma.
Footnotes: [a] To avoid the impact of bridging therapy on tumour burden for patients in TRANSCEND, tumour burden SPD from screening was used for patients who received bridging therapy, and tumour burden SPD from before lymphodepleting chemotherapy was used for patients who did not receive bridging therapy. INV-assessed SPD was used. [b] Represents values reported in Locke (2019).[138] [c] Baseline neutropenia, thrombocytopenia, and anaemia were assessed by laboratory values according to CTCAE v4.03. Data for TRANSCEND were from screening and those for ZUMA-1 were from before lymphodepleting chemotherapy. DCO: 19 June 2020 for TRANSCEND. * Baseline characteristics from TRANSCEND were rederived according to ZUMA-1 definitions and categorizations as needed. Criteria that were rederived are noted within the table.
Source: BMS Data on File (MAIC Report 2025; Table 6);[136] Liso-cel SmPC.[2]

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Outcomes

Efficacy outcomes evaluated and presented herein were PFS, and OS. The definitions for PFS and OS were similar, with both trials capturing INV- and the IRC-assessed PFS. PFS data was reported based on both FDA and EMA censoring rules in the TRANSCEND trial; however, only FDA censoring rules were reported for ZUMA-1. Thus, the MAIC analyses conducted for liso-cel vs. axi-cel are all based on FDA censoring rules.

Safety outcomes of interest for the feasibility assessment were the following AESIs:

- Any TEAEs:
    - Grade ≥3 TEAEs
    - Grade 5 TEAEs
- CRS: graded by Lee 2014 or University of Pennsylvania (UPenn) criteria
- Neurologic events, neurotoxicity (NT), encephalopathy and aphasia
- Infections: high-level group terms per infections and infestations SOC
- Hypogammaglobulinaemia: grouped preferred terms assessed as AEs by INVs
- Prolonged cytopenias:
    - Prolonged cytopenia: Grade ≥ 3 neutropenia, anaemia, or thrombocytopenia unresolved at Day 29 (liso-cel) or Day 30 (axi-cel) by laboratory assessment
    - Prolonged anaemia: Grade ≥ 3 ongoing at Day 29 (liso-cel) or Day 30 (axi-cel) reported as an AE
    - Prolonged neutropenia: Grade ≥ 3 ongoing at Day 29 (liso-cel) or Day 30 (axi-cel) reported as an AE
    - Prolonged thrombocytopenia: Grade ≥ 3 ongoing at Day 29 (liso-cel) or Day 30 (axi-cel) reported as an AE
- Febrile neutropenia: preferred term

Of note, study-defined NT included all TEAEs considered potential manifestations of CAR T cell associated NT (i.e. ICANS). They were evaluated using a study-defined approach and were identified by trial investigators who were trained in their recognition and management. As such, study-defined NT may not be directly comparable due to definition differences among the studies.

Summary

A comparison of the study design, eligibility criteria, and baseline characteristics of patients in the TRANSCEND and ZUMA-1 trials demonstrated sufficient similarities to permit an indirect comparison. However, notable differences between the trials necessitated the use of a MAIC to minimise bias when comparing liso-cel with axi-cel. Large differences in the definitions or categorizations of patient characteristics such as IPI score, disease histology, number of prior lines of therapy, and R/R to last therapy between trials were reduced by redefining the variables within the liso-cel IPD to align more closely to those in the comparator study.

Investigation of outcome definitions and data availability indicated that MAICs are feasible for both key efficacy outcomes (i.e., PFS, and OS). For AESI, MAICs are feasible for Grade 3 or 4 TEAEs, CRS, study-defined NT, NEs per ND/PD SOC, study-defined NT of encephalopathy, encephalopathy per ND/PD SOC, study-defined NT of aphasia, aphasia per ND/PD SOC, infections, hypogammaglobulinaemia, and febrile neutropenia in comparisons of liso-cel to axi-cel. MAICs of Grade ≥ 3 and Grade 5 TEAEs are possible for liso-cel versus axi-cel.

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B.3.9.4 Methodology

Naïve comparisons of efficacy outcomes between trials typically introduce bias because of differences (unmatched and unadjusted) in baseline demographic and clinical characteristics, which are either prognostic or treatment-effect modifiers. When there are considerable differences in patient and study characteristics, analysis using IPD may be required. In these situations, MAICs are commonly used to derive relative treatment effects, in line with the guidance provided in NICE technical support document (TSD) 18.[143] Notably, MAICs have been used to compare efficacy and safety profiles for axi-cel in B-cell lymphoma and for treatments in other disease areas and between treatments in other disease areas.[144-147]

Given the open-label, single-arm trial design, an anchored MAIC is not an option and, as such, an unanchored MAIC was conducted, in line with the guidance provided in NICE technical support document (TSD) 18.[143] The validity of inferences drawn from such comparisons is based on the assumption that all relevant prognostic factors have been incorporated in the MAIC. Although it is virtually impossible to adjust for all possible factors that may differ between trials, adjustment for most known, clinically relevant prognostic factors can help alleviate the risk of bias associated with relative treatment effects obtained via unanchored MAIC.[148]

Individual patient data (IPD) from TRANSCEND were adjusted to match the marginal distribution (e.g., mean, variance) of clinical factors among patients from the ZUMA-1 trial. Patients from TRANSCEND were removed from the IPD set if they did not satisfy eligibility criteria specified in the comparator trial for each MAIC. Individual patient-level data for patients who remained in the TRANSCEND data set were weighted using a method-of-moments propensity score model. Baseline characteristic and outcome definitions were aligned with those in ZUMA-1. Clinically relevant prognostic factors (identified from literature, TRANSCEND data, and 5 external clinical experts) were adjusted collectively in a stepwise fashion by ranked order.

The MAIC included a rigorous, multi-faceted process to identify and rank-order clinically relevant factors. The process involved a comprehensive review of the literature, analysis of the TRANSCEND database, and the establishment of a panel of five clinical experts across five regions (Canada, France, Germany, the UK and the United States). Interviews with clinical experts at several stages – both agnostic to the data and presented with the data – lead to the identification of an exhaustive list of clinical factors confirmed to be relevant to LBCL and CAR T-cell therapy. Clinical experts rank-ordered factors from most to least important to include within the model, which, when paired with data-driven rankings, resulted in a final list of an evidence-informed ranking of factors. Ranking was performed separately for each outcome, acknowledging the fact that some factors may be more important to balance for certain outcomes.

Efficacy outcomes

In total, ten clinical factors were included in the primary analysis (Table 32). Five of the clinical factors were related to trial eligibility criteria and treatment protocol, and so these factors were used first as matching criteria in the MAIC (Table 31). An additional five clinical factors (tumour burden, IPI score, R/R to last therapy, bulky disease, and creatinine clearance for PFS or age for OS) were adjusted in the primary analysis to reduce residual imbalances between studies among matched patients. These five factors varied across outcomes based on evidence-informed clinical rankings.

A key factor that differed between the trials was whether bridging therapy was permitted. ZUMA-1 did not permit bridging therapy prior to infusion, whereas TRANSCEND allowed bridging at the investigator's discretion.

As discussed in NICE TA1048, this difference could indicate that patients with fast-progressing disease may be less likely to be enrolled in the ZUMA-1 trial and, as a result, the infused population in

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ZUMA-1 may represent a fitter subset of patients who were able to proceed without bridging. In comparison, the majority of patients in the TRANSCEND trial required bridging therapy ([redacted]%).[126] As such, patients from TRANSCEND who received bridging therapy were removed from the primary analysis in order to reduce confounding by bridging status. Sensitivity analysis not matching on the use of bridging therapy were also conducted, as detailed below.

Table 31: Clinical Factors Matched for Efficacy outcomes in Liso-cel versus Axi-cel Comparisons

Variable	Liso-cel vs. Axi-cel
Disease histology	Patients with FL3B were removed
Prior allo-HSCT	Patients who had received prior allo-HSCT were removed
ECOG PS	Patients with ECOG PS of 2 were removed
Secondary CNS involvement	Patients with secondary CNS involvement were removed
Bridging therapy	Patients who received bridging therapy were removed

Abbreviations: Allo-HSCT: allogenic haematopoietic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group performance status Liso-cel: lisocabtagene maraleucel; FL3B: follicular lymphoma grade 3B.
Source: BMS Data on File (MAIC Report 2025; Table 11).[136]

The following sensitivity analyses were also performed:

- Sensitivity analysis 1 (SA1): A repeat of the primary analysis but removing bridging therapy as a matching factor (Table 32). This was conducted to help assess the effect of bridging therapy on results, recognising that the receipt of bridging therapy could be related to other factors associated with aggressive disease.
- Sensitivity analysis 2 (SA2): As per SA1, plus adjusting for seven additional factors (Table 32). This was conducted to assess the effect of balancing more factors after gaining ESS upon excluding bridging therapy.

Table 32: Clinical Factor Adjusted for Efficacy Outcomes for all analyses of Liso-cel versus Axi-cel

		PFS			OS		
	Clinical Factor	**Pri.**	**SA1**	**SA2**	**Pri.**	**SA1**	**SA2**
Factors matched (as per Table 31)	Bridging therapy	✓			✓		
	Disease histology	✓	✓	✓	✓	✓	✓
	ECOG PS	✓	✓	✓	✓	✓	✓
	Secondary CNS involvement	✓	✓	✓	✓	✓	✓
	Prior allo-HSCT	✓	✓	✓	✓	✓	✓
Factors adjusted (5 factors adjusted in primary analysis and SA1, 7	Tumour burden	✓	✓	✓	✓	✓	✓
	IPI score	✓	✓	✓	✓	✓	✓
	R/R to last therapy	✓	✓	✓	✓	✓	✓
	Bulky disease	✓	✓	✓	✓	✓	✓
	Age			✓	✓	✓	✓

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		PFS			OS		
	Clinical Factor	**Pri.**	**SA1**	**SA2**	**Pri.**	**SA1**	**SA2**
additional factors adjusted in SA2)	Prior auto-HSCT			✓			✓
	Disease stage			✓			✓
	CrCl	✓	✓	✓			✓
	Extranodal disease			✓			✓
	No. prior therapies			✓			✓
	Sex			✓			✓
	Absolute lymphocyte count			✓			✓
	LVEF			✓			✓

Abbreviations: Allo-HSCT: allogenic haematopoietic stem cell transplant; Auto-HSCT: autologous haematopoietic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; Liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; No.: number; OS: overall survival; PFS: progression-free survival; Pri.: primary analysis; R/R: relapsed or refractory; SA1: sensitivity analysis 1; SA2: sensitivity analysis 2.
Source: BMS Data on File (MAIC Report 2025; Table 12).[136]

Safety outcomes

Analyses of AESIs were conducted only for patients who did not receive bridging therapy (i.e., bridging therapy factor included, aligned with primary analysis of the efficacy analysis). In total, nine clinical factors were included.

Four of the clinical factors were related to trial eligibility criteria and treatment protocol; hence, TRANSCEND IPD was first matched to the ZUMA-1 trial for these factors across all AESI (Table 33). Five additional clinical factors were then adjusted to minimise differences between studies in the remaining patients according to the final rank-order for all AESI (baseline Grade ≥3 anaemia, neutropenia, and thrombocytopenia; pre-lymphodepleting chemotherapy; tumour burden and number of prior lines of therapy).

Table 33: Factors Matched for AESIs in Liso-cel versus Axi-cel Comparisons

Variable	Liso-cel versus Axi-cel
Secondary CNS involvement	Patients with secondary CNS involvement were removed
ECOG PS	Patients with ECOG PS of 2 were removed
Prior allo-HSCT	Patients who had received prior allo-HSCT were removed
Bridging therapy	Patients who received bridging therapy were removed

Abbreviations: AESI: adverse events of special interest; Allo-HSCT: allogenic haematopoietic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group performance status Liso-cel: lisocabtagene maraleucel.
Source: BMS Data on File (MAIC Report 2025; Table 11).[136]

B.3.9.5 Results

Clinical factors at baseline

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Overall, some of the unadjusted (or naïve) clinical factors at baseline were [redacted] ([redacted]% of factors with SMD <0.2) between liso-cel and axi-cel. In both the primary and sensitivity analyses, matching and adjusting patients from TRANSCEND to the ZUMA-1 population produced [redacted] of clinical factors between studies. For example, in the primary analysis of OS, the proportion of well-matched clinical factors [redacted] [redacted]% (unadjusted) to [redacted]% (primary analysis). A summary of comparing naïve and matched factors for OS is presented in Table 34.

Similarly, after matching and adjusting AESIs, the proportion of well-matched clinical factors [redacted]% (in naïve dataset) to [redacted]% factors achieving SMDs <0.2.

Table 34: Comparison of Clinical Factors and SMDs Before and After MAIC for Primary Analysis of OS for Liso-cel and Axi-cel

Clinical Factor	Axi-cel (ZUMA-1) Phase 2 Analysis Set	Liso-cel (TRANSCEND) DLBCL Cohort Efficacy Set (DL1+DL2 subgroup) Overall Survival			
		Before MAIC (naïve)		After MAIC (Primary)	
N or ESS	**N=101**	**N=216**		**ESS=[redacted]**	
			SMD		**SMD**
Age					
Mean (SD)	56.3 (12.0)	[redacted]	[redacted]	[redacted]	[redacted]
Sex, %					
Male	67.3	[redacted]	[redacted]	[redacted]	[redacted]
IPI Score, per ZUMA-1 Categorisation, %					
0 to 2	54.5	[redacted]	[redacted]	[redacted]	[redacted]
3 to 4	45.5	[redacted]		[redacted]	
5	0	[redacted]		[redacted]	
Missing	0	[redacted]		[redacted]	
ECOG PS at Screening, %					
0	41.6	[redacted]	[redacted]	[redacted]	[redacted]
1	58.4	[redacted]		[redacted]	
2	0	[redacted]		[redacted]	
Disease Stage, %					
I or II	14.9	[redacted]	[redacted]	[redacted]	[redacted]
III or IV	85.1	[redacted]		[redacted]	
Missing	0	[redacted]		[redacted]	
Tumour Burden based on SPD before Lymphodepleting Chemotherapy, INV-assessed (cm^2)					
Mean (SD)	50.4 (43.7)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary CNS Involvement at Time of Treatment, %					
No	100	[redacted]	[redacted]	[redacted]	[redacted]
Yes	0	[redacted]		[redacted]	
Extranodal Disease, %					
No	30.7	[redacted]	[redacted]	[redacted]	[redacted]
Yes	69.3	[redacted]		[redacted]	

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Clinical Factor	Axi-cel (ZUMA-1) Phase 2 Analysis Set	Liso-cel (TRANSCEND) DLBCL Cohort Efficacy Set (DL1+DL2 subgroup) Overall Survival			
		Before MAIC (naïve)		After MAIC (Primary)	
N or ESS	**N=101**	**N=216**		**ESS=[redacted]**	
			SMD		**SMD**
Missing	0	[redacted]		[redacted]	
Bulky Disease, %					
No	83.2	[redacted]	[redacted]	[redacted]	[redacted]
Yes	16.8	[redacted]		[redacted]	
Missing	0	[redacted]		[redacted]	
Disease Histology, per ZUMA-1 Categorisation, %					
DLBCL	76.2	[redacted]	[redacted]	[redacted]	[redacted]
DLBCL tFL	15.8	[redacted]		[redacted]	
PMBCL	7.9	[redacted]		[redacted]	
FL3B	0	[redacted]		[redacted]	
Number of Prior Lines of Therapy, Per ZUMA-1 Definition, %					
1	3.0	[redacted]	[redacted]	[redacted]	[redacted]
2	27.7	[redacted]		[redacted]	
3+	69.3	[redacted]		[redacted]	
Prior HSCT, %					
Allo-HSCT	0	[redacted]	[redacted]	[redacted]	[redacted]
Auto-HSCT	24.8	[redacted]	[redacted]	[redacted]	[redacted]
Bridging Therapy, %					
No	100	[redacted]	[redacted]	[redacted]	[redacted]
Yes	0	[redacted]		[redacted]	
Relapsed or Refractory to Last Therapy, per ZUMA-1 Definition, %					
Relapsed	20.8	[redacted]	[redacted]	[redacted]	[redacted]
Refractory	79.2	[redacted]		[redacted]	
Missing	0	[redacted]		[redacted]	
CrCl Prior to Lymphodepleting Chemotherapy, per ZUMA-1 Eligibility Criteria, %					
< 60 mL/min	0	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 mL/min	100	[redacted]		[redacted]	
LVEF at Screening, per ZUMA-1 Eligibility Criteria, %					
<50%	0	[redacted]	[redacted]	[redacted]	[redacted]
≥50%	100	[redacted]		[redacted]	
<0.1	0	[redacted]	[redacted]	[redacted]	[redacted]
≥0.1	100	[redacted]		[redacted]	
Missing	0	[redacted]		[redacted]	
Statistics					

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Clinical Factor	Axi-cel (ZUMA-1) Phase 2 Analysis Set	Liso-cel (TRANSCEND) DLBCL Cohort Efficacy Set (DL1+DL2 subgroup) Overall Survival			
		Before MAIC (naïve)		After MAIC (Primary)	
N or ESS	N=101	N=216		ESS=[redacted]	
			SMD		SMD
% of Factors with SMD <0.2	-	[redacted]	[redacted]	[redacted]	[redacted]
% of Factors with SMD <0.1	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: "-": not applicable; ALC: absolute lymphocyte count; Allo-HSCT: allogenic haematopoietic stem cell transplant; Auto-HSCT: autologous haematopoietic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; CrCl: creatinine clearance; DL1D: dose level 1 double-dose schedule; DL1S: dose level 1 single-dose schedule; DL2S: dose level 2 single-dose schedule; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; FL3B: follicular lymphoma grade 3B; INV: investigator; IPI: International Prognostic Index; Liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; MAIC: matching-adjusted indirect comparison; PMBCL: Primary mediastinal B-cell lymphoma; SD: standard deviation; SPD: sum of product of perpendicular diameters; tFL: DLBCL transformed from follicular lymphoma.
Source: BMS Data on File (MAIC Report 2025; Table 13).[136]

Efficacy

Efficacy analyses were conducted for patients using the DLBCL Efficacy Set DL1+DL2 from TRANSCEND for liso-cel and the Phase 2 mITT set from ZUMA-1 for axi-cel. PFS censored according to FDA censoring rules was used for both treatments. As discussed in Section B.3.9.2, PFS and OS are considered the key efficacy outcomes, in alignment with the key outcomes included in the cost-effectiveness model in NICE TA872 and, as such, are the only efficacy outcomes from the MAIC presented within this section. MAIC results for ORR and CRR are presented within the MAIC report included within the reference pack accompanying this submission.[136]

Bridging therapy is a key prognostic factor, given that patients requiring bridging may have more aggressive/fast-progressing disease compared with those who receive a CAR T infusion without bridging therapy, as discussed in NICE TA1048.[60] This difference could indicate that patients with fast-progressing disease may be less likely to be enrolled in the ZUMA-1 trial and, as a result, the population in ZUMA-1 may represent a fitter subset of patients who were able to proceed without bridging. While the use of bridging therapy may improve disease control prior to CAR T cell infusion, providing a response benefit and decreased severe toxicity, it has been suggested that patients who require bridging therapy may have inferior outcomes compared with those who do not as these patients tend to have bulkier, more rapidly progressive, or symptomatic disease compared with patients who do not receive bridging therapy.[149] As such, the primary analysis has accounted for this imbalance to avoid confounding and any misinterpretation of efficacy results.

The results of the MAIC showed [redacted] between liso-cel versus axi-cel in the rate of disease progression or mortality (PFS; HR: [redacted][primary analysis]) or the rate of mortality (OS; HR: [redacted][primary analysis]) across the analyses. These conclusions are also in line with the results of the original published MAIC.[137]

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PFS

The naïve comparison of TRANSCEND versus ZUMA-1 demonstrated [redacted] in the rate of disease progression or death for liso-cel compared with axi-cel (Table 35; HR: [redacted]).

The same conclusion was observed in the primary MAIC analysis, which matched and adjusted for 10 factors, including bridging therapy (Section B.3.9.4). The rate of disease progression or death was [redacted] between liso-cel and axi-cel (HR: [redacted]). These results were consistent across SA1 and SA2 which did not match for bridging therapy, with [redacted] in rate of disease progression or mortality between liso-cel and axi-cel.

Table 35: Summary of MAIC Results for PFS in the Comparison of Liso-cel to Axi-cel

	Axi-cel (ZUMA-1)		Liso-cel (TRANSCEND) DLBCL Cohort Efficacy Set (DL1+DL2 subgroup)		Liso-cel vs. Axi-cel	
Analyses	**N**	**Median, months (95% CI)[a]**	**N/ESS**	**Median, months (95% CI)**	**HR (95% CI)**	**p-value**
Naïve	101	5.9 (3.7, 18.4)[a]	216	[redacted]	[redacted]	[redacted]
Primary			[redacted]	[redacted]	[redacted]	[redacted]
SA1			[redacted]	[redacted]	[redacted]	[redacted]
SA2			[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel: axicabtagene ciloleucel; CI: confidence interval; ESS: effective sample size; HR: hazard ratio; IPD: individual patient data; Liso-cel: lisocabtagene maraleucel; MAIC: matching-adjusted indirect comparison; N: number; NR: not reported; SA: sensitivity analysis.
Footnotes: [a] The median was obtained from pseudo-IPD based on digitized KM curve. [b] DCO: 28th September 2021.
Source: BMS Data on File (MAIC Report 2025; Table 16).[136]

KM curves for the primary analysis are presented in Figure 10. Overall, the KM curves for all analyses demonstrated [redacted]. Visual inspection of the KM curve and the Grambsch-Therneau test was generally supportive of the proportional hazards assumption for these analyses.

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Figure 10: Comparison Kaplan-Meier Curves of PFS between Liso-cel and Axi-cel (MAIC Primary Analysis; ESS=[redacted])

Abbreviations: Axi-cel: axicabtagene ciloleucel; ESS: effective sample size; Liso-cel: lisocabtagene maraleucel; PFS: progression-free survival.
Source: BMS Data on File (MAIC Report 2025 – Figure 4).[136]

OS

The naïve comparison showed [redacted] in OS between liso-cel and axi-cel (HR: [redacted]). Similarly, in the primary analysis, [redacted] in OS between liso-cel and axi-cel were observed (HR: [redacted]). These results were consistent across SA1 and SA2 which did not match for bridging therapy, with [redacted] in rate of mortality between liso-cel and axi-cel.

Table 36: Summary of MAIC Results for OS in the Comparison of Liso-cel to Axi-cel

	Axi-cel (ZUMA-1)		Liso-cel (TRANSCEND) DLBCL Cohort Efficacy Set (DL1+DL2 subgroup)		Liso-cel vs. Axi-cel	
Analyses	**N**	**Median, months (95% CI)[a]**	**N/ESS**	**Median, months (95% CI)**	**HR (95% CI)**	**p-value**
Naïve	101	25.7 (12.8, NR)[a]	216	[redacted]	[redacted]	[redacted]
Primary			[redacted]	[redacted]	[redacted]	[redacted]
SA1			[redacted]	[redacted]	[redacted]	[redacted]
SA2			[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel: axicabtagene ciloleucel; CI: confidence interval; ESS: effective sample size; HR: hazard ratio; IPD: individual patient data; Liso-cel: lisocabtagene maraleucel; MAIC: matching-adjusted indirect comparison; N: number; NR: not reached; SA: sensitivity analysis.
Footnotes: [a] The median was obtained from pseudo-IPD based on digitised KM curve from DCO: 11th August 2021. [b] DCO: 31st January 2024.
Source: BMS Data on File (MAIC Report 2025; Table 17).[136]

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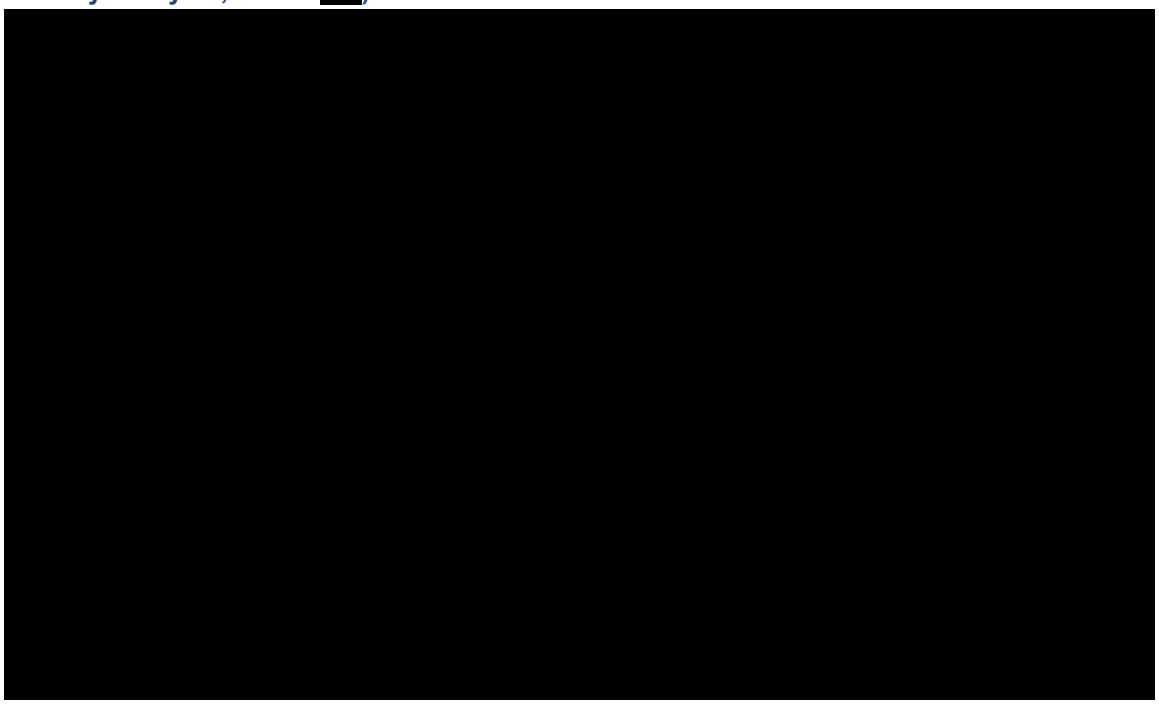
KM curves for the primary analysis are presented in Figure 11. Overall, the KM curves for all analyses demonstrated [redacted]. Visual inspection of the KM curve and the Grambsch-Therneau test was generally supportive of the proportional hazards assumption for these analyses.

Figure 11: Comparison of Kaplan-Meier Curves of OS between Liso-cel and Axi-cel (MAIC Primary Analysis; ESS = [redacted])



Abbreviations: Axi-cel: axicabtagene ciloleucel; ESS: effective sample size; Liso-cel: lisocabtagene maraleucel; OS: overall survival.
Source: BMS Data on File (MAIC Report 2025 – Figure 9).[136]

Safety

Safety analyses of AESIs were conducted using the DL1+DL2 subgroup of the DLBCL Cohort Treated Set from TRANSCEND for liso-cel and Phase 1 + 2 safety analysis set from ZUMA-1 or axi-cel. After matching and adjusting for 9 clinical factors (Section B.3.9.4), including removing patients from TRANSCEND who received bridging therapy, liso-cel had an ESS of [redacted] (Table 37).

Overall, the results of the MAIC demonstrate that liso-cel is associated with [redacted] of AESIs occurring than axi-cel, owing to the more favourable safety profile of liso-cel compared with axi-cel. These include, but are not limited to, [redacted] of Grade ≥3 TEAEs overall, as well as all-grade and Grade ≥3 CRS, all-grade and Grade ≥3 study-defined NT and all-grade hypogammaglobulinaemia. These conclusions are also in line with the results of the original published MAIC.[137]

There are several factors that could contribute to the more favourable safety profile observed with liso-cel as compared with axi-cel, including the 4-1BB co-stimulatory domain, which is reportedly associated with a lower incidence of CRS and NE AEs than CD28-containing construct.[150] In addition, as variability in total and $CD8^+$ CAR T cells has been associated with increased toxicity, the administration of liso-cel at a defined composition with consistent total and relative doses of $CD8^+$:$CD4^+$ CAR^+ T cells may also contribute to reduced toxicity.[24, 151]

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Table 37: Summary of MAIC Results for AESI in the Comparison of Liso-cel to Axi-cel

		Axi-cel (ZUMA-1) Phase 1+2 Safety Analysis Set	Liso-cel (TRANSCEND) DLBCL Cohort Treated Set (DL1+DL2 subgroup)		Liso-cel vs. Axi-cel OR (95% CI)			
AESI*	**Grades**	**Reported Rates, %**	**Naïve, %**	**MAIC, %**	**Naïve**	**P-value**	**MAIC**	**P-value**
N / ESS		**N=108**	**N=229**	**ESS=** [redacted]				
Any TEAEs	Grade ≥3	98.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade 3 or 4	89.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade 5	8.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRS, Lee 2014 Criteria	All grades	92.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	11.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT, per Study Protocol	All grades	66.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	32.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NE, per ND/PD SOC	All grades	87.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	31.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy, per Study Protocol, Grouped Term	All grades	37.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	23.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy, per ND/PD SOC, Grouped Term	All grades	58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia, per Study Protocol, Grouped Term	All grades	17.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3[a]	7.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia, per ND/PD SOC, Grouped Term	All grades	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3[a]	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections, Any Pathogens, per Infections and Infestations SOC	Grade ≥3	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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		Axi-cel (ZUMA-1) Phase 1+2 Safety Analysis Set	Liso-cel (TRANSCEND) DLBCL Cohort Treated Set (DL1+DL2 subgroup)		Liso-cel vs. Axi-cel OR (95% CI)			
AESI*	**Grades**	**Reported Rates, %**	**Naïve, %**	**MAIC, %**	**Naïve**	**P-value**	**MAIC**	**P-value**
N / ESS		**N=108**	**N=229**	**ESS=[redacted]**				
Hypogammaglobulinaemia[b], Grouped Term	All grades	16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged Cytopenia, Laboratory Assessment	Grade ≥3	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged Anaemia, AE[c]	Grade ≥3	10.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged Neutropenia, AE[c]	Grade ≥3	25.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged Thrombocytopenia, AE[c]	Grade ≥3	24.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile Neutropenia, as Preferred Term	All grades	36.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Grade ≥3	32.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: "-": not applicable; AE: adverse event; AESI: adverse events of special interest; Axi-cel: axicabtagene ciloleucel; CI: confidence interval; CRS: cytokine release syndrome; ESS: effective sample size; INV: investigator; Liso-cel: lisocabtagene maraleucel; MAIC: matching-adjusted indirect treatment comparison; N: sample size; ND: neurologic disorder; NE: neurologic-related events; NR: not reported; NT: neurotoxicity; OR: odds ratio; PD: psychiatric disorder; SOC: system organ class; TEAE: treatment-emergent adverse event.
Footnotes: [a] MAICs not possible because all Grade ≥ 3 patients would have been excluded during matching. [b] Represents TEAE assessed by INV. [c] Prolonged cytopenia is defined as Grade ≥3 anaemia, neutropenia, or thrombocytopenia present at Day 29 (liso- cel) or Day 30 (axi-cel). * TEAE reported unless otherwise specified.
Source: BMS Data on File (MAIC Report 2025; Table 18).[136]

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B.3.9.6 Uncertainties in the indirect and mixed treatment comparisons

Limitations of the MAIC include those inherent to an unanchored ITC. Despite the rigorous methodology used to identify and rank clinical factors, there is no assurance that all factors relevant to each outcome were captured. Furthermore, some factors deemed important were not reported for ZUMA-1 in a format that allowed comparison or alignment with TRANSCEND. In such cases, the balance of these factors between studies cannot be measured and relies on the correlation of included factors used for matching and adjustment. Though the most important factors were included, their inclusion does not guarantee compensation for unrepresented factors, leaving the estimated relative treatment effects potentially subject to an unknown degree of bias. Additionally, for the available factors, given the degree of imbalance among the two trials, it was not feasible to match and adjust on all identified factors. Though rank-ordering the factors helped to prioritise the most important factors, only a subset could be included. Despite these limitations, the results and conclusions were consistent between primary and sensitivity analyses, demonstrating the robustness of the analyses.

Additionally, a key limitation of the MAIC is inherent to the evidence base for this submission, in that the majority of patients in TRANSCEND received bridging therapies ([redacted]%), whilst bridging therapy was not permitted in ZUMA-1. As patients requiring bridging therapy often have more aggressive/fast-progressing disease and typically have inferior treatment outcomes, the lack of bridging therapy permitted in ZUMA-1 suggests this trial may represent a fitter subset of patients (Section B.3.9.5).[60, 149] This is reflected in the differences in median OS and PFS between analyses that excluded patients who received bridging therapy (the primary analysis) and those that included all patients regardless of bridging therapy (naïve, SA1 and SA2). The median OS and PFS for liso-cel were [redacted] in SA1 compared to the primary analysis (mOS: [redacted]months versus [redacted]months; mPFS:[redacted]months versus [redacted]months, respectively) despite matching and adjusting for the same factors other than bridging therapy. As such, any analyses that do not adjust for bridging therapy could be biased towards axi-cel, based on a ZUMA-1 trial population with a potentially improved prognosis.

After excluding patients who received bridging therapy in the primary analysis, the overlap between the TRANSCEND and ZUMA-1 trials was [redacted]. This resulted in a [redacted] liso-cel ESS compared with the overall trial population in TRANSCEND in both PFS and OS analyses (ESS: [redacted] and [redacted], respectively). The primary analysis was designed to balance clinical factors, patient weights, and inter-study comparability. Therefore, it is important to consider the clinical rationale for excluding bridging therapy (as outlined above) when assessing the appropriateness of the primary analysis. The primary analysis was selected to adjust for key clinical factors, including bridging therapy. The sensitivity analyses did not adjust for bridging therapy and therefore, retained a [redacted] ESS, whilst producing results consistent with the primary analysis, showing [redacted] in efficacy between liso-cel and axi-cel.

B.3.9.7 Conclusions of MAIC

The MAIC has provided comparative efficacy and safety evidence for liso-cel versus axi-cel, in the 3L+ treatment of patients with R/R LBCL. Overall, after matching and adjusting for key clinical prognostic factors and treatment-effect modifiers, liso-cel was found to be associated with comparable efficacy to axi-cel, and a more favourable safety profile. These conclusions were consistent across the primary analyses, which adjusted for bridging therapy, and sensitivity analyses which did not adjust for bridging therapy, but adjusted for additional prognostic factors. These conclusions are also in line with the results of the original published MAIC, and supported by feedback from UK CAR T Experts.[11, 137]

The results of the MAIC assessing safety outcomes demonstrated that liso-cel has a more favourable safety profile compared with axi-cel. This finding is in line with feedback from UK CAR T Experts in

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TA1048, who noted that patients receiving liso-cel experience fewer AEs compared with those receiving axi-cel, particularly in relation to CRS and neurotoxicity, including ICANS.[60] Further support for the comparable efficacy and favourable safety profile of liso-cel compared with axi-cel is available from multiple US RWE studies, where liso-cel is recommended for routine practice.[12-14] Through its improved safety profile compared with axi-cel, liso-cel is associated with fewer ICU admissions (Section B.1.3.2). Another downstream implication is that liso-cel has the potential to be delivered in the outpatient setting, based on promising efficacy data from the outpatient delivery of liso-cel at 3L+ in TRANSCEND-OUTREACH-007 (see Section B.3.6.1.3).[110] The introduction of a less toxic, efficacious treatment option at 3L+, would aid in reducing some of the existing economic, HRQoL and resource burden.

On the basis of comparable efficacy, liso-cel is suitable for consideration through a cost-comparison approach versus axi-cel, and is likely to provide improved health benefits given the more favourable safety profile associated with liso-cel.

B.3.10 Adverse reactions

B.3.10.1 TRANSCEND

B.3.10.1.1 Summary of adverse events

Safety analyses using the DLBCL Cohort Treated Set (N=270; see Section B.3.3.3,Table 9), demonstrated an acceptable safety profile of liso-cel in the treatment setting. Full details on the safety analysis set are presented in Table 9 (Section B.3.3.2). Treatment-emergent AEs (TEAEs) are presented for the DL1+DL2 dosing regimen. Posttreatment-emergent AEs are presented for the total DLBCL Cohort Efficacy Set across all dose levels (Appendix J).

AE are presented according to when they occurred:

- TEAEs were defined as any AEs that occurred from the start of liso-cel treatment, up to 90 days after the last dose
- The posttreatment-emergent period was also analysed (GC-LTFU-001; DCO: 31st January 2024). It started 91 days after the last liso-cel dose, or earlier if the patient started another cancer treatment or received liso-cel again before day 91.[59]

A summary of AEs and AESI are presented in Table 38. At the September 2021 DCO, [redacted]% of patients had experience TEAEs. The most common treatment-emergent AESI were prolonged cytopenia ([redacted]%) and CRS ([redacted]). CRS and NT are recognised toxicities associated with CAR T-cell therapies and occurred in [redacted] of patients treated with liso-cel (CRS or NT [redacted]%; CRS [redacted]%; NT [redacted]%).[120] This is notable given that CRS and NT events typically require ICU admission (see Section B.4.2.3). Further details of specific TEAEs considered related to liso-cel are presented in Appendix J and additional treatment-emergent AESIs can be found in the 2021 Addendum CSR provided in the reference pack included alongside this submission.[120]

Posttreatment-emergent AEs, including data from GC-LTFU-001 are reported in Appendix J. There were no new clinically meaningful safety findings reported in the posttreatment-emergent period, with a median follow-up of [redacted] days.[59]

The proportion of patients requiring hopsitalisations and ICU stays in the TRANSCEND trial are presented in Table 39. In the [redacted] ([redacted]%) patients who received the DL1+DL2 dosing regimen of liso-cel as an inpatient, [redacted] were admitted to ICU (median duration = [redacted] days [range: [redacted]]). For those that received liso-cel in an outpatient setting (N=[redacted]%]),[redacted] patient was admitted to ICU for [redacted] days.[59]

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Table 38: Summary of adverse events (TRANSCEND; DLBCL Cohort Treated Set; 28th September 2021 DCO)

	DL1+DL2 (N=229)
TEAEs, n(%)	
Any Grade	[redacted]
Grade ≥3	[redacted]
Grade 5	[redacted]
Serious AE	[redacted]
Treatment-emergent AESIs, n(%)	
Cytokine release syndrome	[redacted]
Neurological toxicity	[redacted]
Prolonged cytopenia	[redacted]
Grade ≥3 infections	[redacted]
Hypogammaglobulinaemia	[redacted]
Infusion-related reaction	[redacted]
Secondary primary malignancy	[redacted]
Tumour lysis syndrome	[redacted]

Abbreviations: AE: adverse event; AESI: adverse event of special interest;; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; TEAE: treatment-emergent adverse event.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 8.1-2)[120]

Table 39: Hospitalisation for inpatients and outpatients (TRANSCEND; DLBCL Cohort Treated Set; September 2021 DCO)

	DL1+DL2 (N=229)
Inpatient liso-cel administration, n(%)	[redacted]
Median length of hospitalisation, days	[redacted]
ICU, n	[redacted]
Median length of ICU stay, days	[redacted]
Outpatient liso-cel administration, n (%)	[redacted]
Hospitalisation following liso-cel treatment, n (%)	[redacted]
Median length of hospitalisation, days	[redacted]
ICU, n	[redacted]
Median length of ICU stay, days	[redacted]

Abbreviation: DCO: data cut off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; ICU: intensive care unit.
Source: BMS Data on File (TRANSCEND Clinical Study Report, May 2024 – Table 14.2.6.1.a)[59]

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B.3.10.1.2 Incidence of adverse events

The most commonly reported Grade ≥3 TEAEs, occurring in ≥2% of patients, are presented in Table 40Table 40.Of the [redacted]patients in the DL1+DL2 analysis set, [redacted]% experienced ≥Grade 3 TEAEs. The most common ≥Grade 3 TEAEs (≥20% of patients) were neutropenia ([redacted]%), anaemia ([redacted]%) and thrombocytopenia ([redacted]%). The incidence of ≥Grade 3 infections were low ([redacted]%).[120]

Table 40: Grade ≥3 TEAEs occurring in ≥2% of patients (TRANSCEND; DLBCL Cohort Treated Set; 28th September 2021 DCO)

	DL1+DL2 (N=229)
Grade ≥3 TEAEs, n(%)	[redacted]
Blood and lymphatic system disorders	[redacted]
Neutropenia	[redacted]
Anaemia	[redacted]
Thrombocytopenia	[redacted]
Leukopenia	[redacted]
Febrile neutropenia	[redacted]
Lymphopenia	[redacted]
Metabolism and nutrition disorders	[redacted]
Decreased appetite	[redacted]
Hypokalemia	[redacted]
Hypophosphatemia	[redacted]
Hyponatremia	[redacted]
Infections and infestations	[redacted]
Pneumonia	[redacted]
Nervous system Disorders	[redacted]
Encephalopathy	[redacted]
Syncope	[redacted]
Vascular disorders	[redacted]
Hypotension	[redacted]
Hypertension	[redacted]
Renal and urinary disorders	[redacted]
Acute kidney injury	[redacted]
Immune system disorders	[redacted]
CRS	[redacted]

Footnotes: The most severe grade is used for those AEs that occur more than once in an individual patient during the study. CRS is graded based on the Lee grading criteria.[152]
Abbreviations: CRS: cytokine release syndrome; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; TEAE: treatment-emergent adverse event.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 8.2.2-1).[120]

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CRS and NT are recognised toxicities associated with CAR T-cell therapies.[153] In the DL1+DL2 cohort of the DLBCL Cohort Treated Set, N= [redacted] ([redacted] had CRS and [redacted] had NT. The median time to onset for any grade CRS was [redacted] days (range: [redacted]). Of the patients that experienced CRS, this AE was resolved in [redacted] patients, with a median time to resolution of first CRS of [redacted] days (range: [redacted]) for resolution of first CRS. The [redacted] patients whose CRS was not resolved had ongoing CRS at the time of death; however, [redacted] death was attributed to CRS.[120] Of the [redacted] patients that experienced any grade NT, the median time to onset was [redacted]days (range: [redacted]) and the median time to resolution was [redacted] days (range: [redacted]). The most frequent AEs identified as NT events were encephalopathy ([redacted] and confusional state ([redacted] As with CRS, out of the [redacted] patients with unresolved NT at the time of death, [redacted]were thought to have died from NT. Full details of treatment-emergent CRS and NT are provided in the 2021 TRANSCEND CSR provided in the reference pack for this submission.[125]

B.3.10.1.3 Deaths

A summary of deaths reported in the DLBCL Cohort Leukapheresis Set (ITT) is presented in Table 41. [redacted] patients died in the DL1 or DL2 dosing regimens of this analysis set died prior to treatment with liso-cel. Of the [redacted]%) of deaths post-infusion, [redacted] ([redacted]%) were due to disease progression.[120] Further details of the periods in which death occurred are presented in Appendix J.4.1.

Table 41: Summary of deaths (TRANSCEND; DLBCL Cohort Leukapheresis Set; 28th September 2021 DCO)

	DL1+DL2 (N=[redacted])
Deaths post liso-cel infusion	[redacted]
Disease progression	[redacted]
AE[a]	[redacted]
Unknown	[redacted]
Other	[redacted]

Footnotes: Patients who did not receive liso-cel or nonconforming product are included only in the DLBCL Cohort Leukapheresis Set displayed in the last column. Last liso-cel infusion includes the latest infusion (either liso-cel or nonconforming product) administered as the single dose in the DL1S, DL2S, or DL3S dose schedule; as the second dose of the DL1D double-dose schedule; or as the last dose of any additional cycles (retreatment cycles are excluded). Deaths that occur after retreatment are reported from the last infusion as defined in the previous sentence.
[a]Three deaths from "other" causes occurred prior to LDC: bowel perforation, cardiogenic shock from cardiomyopathy, and CNS lymphoma (primary reason) and sepsis. Nine deaths from "other" causes occurred post liso-cel treatment: cardiac arrest, stroke unrelated to study, pneumonia, respiratory failure due to pneumonia, disseminated aspergillosis, septic shock, heart attack, sepsis and pneumonia, and diffuse intra-abdominal ischemia.
.**Abbreviations:** AE: adverse event; DCO: data cut-off; DL: dose level.
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021 – Table 6)[120]

B.3.10.2 GC-LTFU-001

Safety analyses from the GC-LTFU-001 study are captured in the posttreatment-emergent AEs for TRANSCEND and TRANSCENDWORLD, presented in Appendix J.5.2 and Appendix K.2.1, respectively.

Posttreatment-emergent AEs in GC-LTFU-001 were generally consistent with TEAEs reported in both the TRANSCEND and TRANSCENDWORLD trials.

B.3.10.3 TRANSCENDWORLD

B.3.10.3.1 Summary of TEAEs

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A summary of TEAEs reported in the Liso-cel Treated Set of TRANSCENDWORLD are presented in Table 42. The TEAEs reported in TRANSCENDWORLD were comparable with those reported in TRANSCEND, further demonstrating the favourable safety profile of liso-cel in patients with R/R LBCL.[120] At the October 2021 DCO, [redacted]% of patients in Cohort 1 had experience TEAEs. The most frequently occurring TEAEs were neutropenia ([redacted]%), anaemia ([redacted]%) and pyrexia ([redacted]%).[125] Further details of the incidence of AEs and deaths are presented in Table 42.

In the posttreatment-emergent period, AEs and SAEs occurred less frequently than in the treatment-emergent period. During this period, [redacted]% of patients reported AEs, including [redacted]% with Grade ≥3 AEs.[125] Full details of the posttreatment-emergent AEs from the TRANSCENDWORLD trial are presented in Appendix K.

Table 42: Summary of TEAEs (TRANSCENDWORLD; Liso-cel Treated Set; October 2021 DCO)

	Cohort 1 (N=[redacted])
TEAEs, n (%)	
Any Grade	[redacted]
Grade ≥3	[redacted]
Grade 5	[redacted]
Serious AE	[redacted]
Treatment-emergent AESIs, n (%)	
Any AESI	[redacted]
CRS	[redacted]
NT	[redacted]
Prolonged cytopenia	[redacted]
Grade ≥3 infections	[redacted]
Macrophage activation syndrome	[redacted]
Hypogammaglobulinaemia	[redacted]
Infusion-related reaction	[redacted]
Secondary primary malignancy	[redacted]
Tumour lysis syndrome	[redacted]
Autoimmune disorder	[redacted]

Abbreviations: AESI: adverse event of special interest; CRS: cytokine release syndrome; DCO: data cut-off; DL: dose level; LDC: lymphodepleting chemotherapy; NT: neurological toxicity; TEAE: treatment-emergent adverse event.
Source: BMS Data on File (TRANSCENDWORLD Clinical Study Report Addendum 01, October 2021 – Table 8.1-2).[125]

B.3.10.4 OUTREACH

B.3.10.4.1 Incidence of AEs

A summary of TEAEs is presented in (Table 43). The incidence of TEAEs were similar between inpatients and outpatients, with the most common TEAEs being neutropenia, leukopenia, CRS and thrombocytopenia. Further details of incidence of AEs are presented in Appendix L.

Similarly to any-Grade TEAEs, the reported Grade ≥3 TEAEs were consistent between inpatients and outpatients (76% and 74%, respectively; Table 43). No Grade 5 TEAEs were reported for either of the patient groups. Fewer patients in the outpatient arm were hospitalised following liso-cel treatment

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compared to the inpatient arm (43 [75%] and 25 [100%], respectively; Appendix L.3), demonstrating that liso-cel can be successfully used in an outpatient setting, lowering the number of days patients spend in hospital. The median duration of initial hospitalisation after liso-cel treatment was 6.0 days (range: 1, 28) for outpatients and 15.0 days (range: 3, 31) for inpatients.[110] Additional results for AESIs, deaths and details of patient hospitalisations are presented in Appendix L.

Table 43: Summary of TEAEs (OUTREACH; Liso-cel Treated Set; June 2022 DCO)

	Outpatients (N=57)	Inpatients (N=25)
Any TEAE, n (%)	57 (100)	25 (100)
Any Grade ≥3 TEAE	42 (74)	19 (76)
Any SAE	33 (58)	15 (60)
CRS or NEs, n (%)		
Any Grade	26 (46)	14 (56)
Grade ≥3	7 (12)	1 (4)

Abbreviations: CRS: cytokine release syndrome; DCO: data cut-off; NE: neurological events; SAE: serious adverse event; TEAE: treatment-emergent adverse event. **Source:** Linhares et al. (2024)[110]

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B.3.11 Conclusions about comparable efficacy and improved safety

Principal findings from the available clinical evidence to support liso-cel

The efficacy of liso-cel in patients with R/R LBCL at 3L+ has been demonstrated in the TRANSCEND trial. This study demonstrated that treatment with liso-cel resulted in a rapid, high rate of durable CR with long-term survival among a broad range of patients with R/R LBCL.

At the most recent DCO (28th September 2021), over half of the patients (53.2%) in the DL1+DL2 group of the DLBCL Cohort Efficacy Set (N=229) achieved a CR to liso-cel, with an ORR based on IRC assessment of 72.7% (Section B.3.6.1.2).[1] Median DoR was 20.5 months (95% CI: 8.2, NR) and the probability of continued response at 24 months was [redacted]%.[1, 120] Median PFS was [redacted] months (95% CI: [redacted]), with a PFS rate of [redacted]% at 24 months (Section B.3.6.1.3) and at the updated DCO (31st January 2024) after a median follow-up of [redacted] months, median OS was [redacted] months (95% CI: [redacted]; Section B.3.6.1.3), indicating the potential for long-term disease-free survival and potential long-term remission.[59, 120] A notable proportion of patients treated with liso-cel demonstrated clinically meaningful improvements in HRQoL at various timepoints across all pre-specified domains of the EORTC-QLQ-C30 and the EQ-5D-5L following treatment with liso-cel.[59] Liso-cel demonstrated clinically meaningful activity across all patient subgroups (Section B.3.7).

Following liso-cel infusion in TRANSCEND, the most frequently reported TEAEs were neutropenia ([redacted]%), anaemia ([redacted]%) and fatigue ([redacted]%). CRS and NT occurred in only [redacted]% and [redacted]% of patients, respectively and the majority of these events were resolved within two weeks (Section B.3.10.1). No Grade 5 CRS or NT were reported.[120] This has the potential to result in quality of life improvements for patients receiving liso-cel compared with axi-cel, although this has not been captured in the economic analysis given the nature of this submission (i.e. cost comparison).

Results from TRANSCEND are supported by the clinical evidence from the TRANSCENDWORLD study (cohort 1: patients with DLBCL NOS, HGL and FL3B, ≥2 lines of therapy), which demonstrated comparable efficacy and safety to TRANSCEND in a global patient population (see Section B.3.6.3). In addition, supportive evidence for the use of liso-cel in an outpatient setting was provided by the OUTREACH trial, demonstrating similar response rates and AE incidence compared to the inpatient setting (Section B.3.6.4; Section B.3.10.4.1).[110]

For comparative efficacy and safety, a MAIC was conducted between liso-cel (TRANSCEND) and axi-cel (ZUMA-1; Section B.3.9). Overall, after matching and adjusting for key clinical prognostic factors and treatment-effect modifiers, liso-cel was found to be associated with comparable efficacy to axi-cel, with [redacted] observed across all analyses. In the primary MAIC analysis, which matched and adjusted for 10 factors, including bridging therapy (Section B.3.9.4), the rate of disease progression or death was [redacted] between liso-cel and axi-cel (HR: [redacted]). Similarly, in the primary analysis for OS, [redacted] between liso-cel and axi-cel were observed (HR: [redacted]). These results were consistent across sensitivity analyses which did not match for bridging therapy. These conclusions are also in line with the results of the original published MAIC, and further supported by feedback from UK CAR T Experts consulted as part of this submission who unanimously agreed that the evidence, so far, have been consistent in showing that liso-cel and axi-cel have comparable efficacy at 3L+.[11, 137] Further support for the comparable efficacy and favourable safety profile of liso-cel compared with axi-cel is available from multiple US RWE studies, where liso-cel is recommended for routine practice.[12-14] One study of 925 patients with R/R LBCL receiving CAR T-cell therapy (of whom 61% received axi-cel and 20% received liso-cel) reported no statistically significant difference in median PFS or OS between liso-cel and axi-cel (p=0.29 and p=0.50, respectively).[13] Additionally, in a study of patients with R/R LBCL who received liso-cel (N=315) or axi-cel (N=963) between April 2022 and October

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2024, a lower proportion of patients receiving liso-cel experienced Grade ≥3 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) among patients receiving liso-cel compared with axi-cel treatment.[14]

The results of the MAIC assessing safety outcomes demonstrated that liso-cel has a more favourable safety profile as compared with axi-cel, with liso-cel being associated with [redacted] of AESIs occurring. These include, but are not limited to, [redacted] odds of Grade ≥3 TEAEs overall, as well as all-grade and Grade ≥3 CRS, all-grade and Grade ≥3 study-defined NT and all-grade hypogammaglobulinaemia. These conclusions are also in line with the results of the original published MAIC.[137] This is in line with discussions in the NICE draft guidance for TA1048, in which clinicians emphasised that the key difference between liso-cel and axi-cel was the safety profile and a US RWE study that reported a lower proportion of patients experiencing Grade ≥3 CRS and ICANS among patients receiving treatment with liso-cel compared with axi-cel.[60] This therefore provides clear evidence demonstrating that liso-cel provides improved health benefits and thus, is suitable for the cost-comparison process versus axi-cel.

Strengths and limitations of the clinical evidence base

TRANSCEND provides evidence for the use of liso-cel in patients with R/R LBCL and demonstrates consistent results across subgroups and histologies. The study is of good-quality, was conducted in accordance with the ethical principles of GCP, and the overall risk of bias was deemed to be low.

UK clinicians considered the TRANSCEND study to provide a strong data package, including a variety of LBCL subtypes, significant proportions of patients aged ≥65 and ≥75 years of age, patients with secondary CNS involvement, those with significant comorbidities including renal impairment, cardiac dysfunction and cytopenias.[120] In addition, the outcomes used in the trial are consistent with those that would be captured as part of standard practice in NHS England. Supplementary LTFU data from the ongoing GC-LTFU-001 trial provide long-term follow up for the OS data on patients in the TRANSCEND trial, with [redacted]% of patients still alive at 84 months (DCO: 31st January 2024).[59]

TRANSCEND was conducted in 14 sites in the US, therefore, no UK patients were enrolled in the study.[120] However, the findings from the TRANSCENDWORLD trial, carried out across 20 sites in 11 countries, generally aligned with those observed in TRANSCEND, indicating that the TRANSCEND results are generalisable to a diverse, global population. In addition, the OUTREACH trial demonstrates that outpatient CAR T-cell therapy with liso-cel is feasible in a community setting, including analysis of 82 patients (57 outpatients, 25 inpatients).[110] As this is an observational study, it can also be considered reflective of real-world practice, supporting the effectiveness of liso-cel outside of a trial setting. This is further supported by a US RWE study on patients with R/R LBCL who received liso-cel (N=315) or axi-cel (N=963) between April 2022 and October 2024, of whom 24% successfully received liso-cel in an outpatient setting, compared with only 5% of patients receiving axi-cel.[14]

A key limitation of each of these trials is that they are single arm. As such, no direct head-to-head evidence comparing liso-cel with the most relevant comparator, axi-cel, is available. In the absence of head-to-head trial data, an ITC analysis, in accordance with NICE TSD18, has been conducted to provide an estimate of liso-cel compared with axi-cel in the relevant patient population (3L+ patients suitable for CAR T; Section B.3.9).[143] Unanchored MAICs require adjustment for all clinically relevant prognostic factors and treatment effect modifiers; an assumption that is generally considered difficult to meet.[148] Although a rigorous, multi-faceted process was used to identify and rank these factors, unrepresented factors may still bias the estimated treatment effects. Nonetheless, the primary and sensitivity analyses were consistent, supporting the robustness of the conclusions.

Additionally, a key limitation of the MAIC is inherent to the evidence base for this submission, in that the majority of patients in TRANSCEND received bridging therapies ([redacted]%), whilst bridging therapy

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was not permitted in ZUMA-1. As patients requiring bridging therapy often have more aggressive/fast-progressing disease and typically have inferior treatment outcomes, the lack of bridging therapy permitted in ZUMA-1 suggests this trial may represent a fitter subset of patients (Section B.3.9.5).[60, 149]

The limited overlap between the TRANSCEND and ZUMA-1 trials with respect to bridging therapy means that the primary analysis MAIC, which adjusted for bridging therapy as a key prognostic factor, resulted in a relatively [redacted] ESS, compared to the overall trial population in TRANSCEND. However, this should be considered to represent a minimal source of uncertainty, as sensitivity analyses which did not adjust for bridging therapy and, therefore, maintained a [redacted] ESS, demonstrated consistent results, showing [redacted] in efficacy between liso-cel and axi-cel. Further support for the comparable efficacy and favourable safety profile of liso-cel compared with axi-cel is available from multiple US RWE studies, where liso-cel is recommended for routine practice, demonstrating that there is no statistically significant difference in median PFS or OS between the two treatments in real-world practice.[13, 14, 108]

B.3.12 Ongoing studies

TRANSCEND, TRANSCENDWORLD and TRANSCEND-OUTREACH are all completed studies, with no further data cuts planned.[118, 123, 124] The GC-LTFU-001 study is ongoing, with no planned additional analyses as of yet.[121] No other studies investigating liso-cel in patients with R/R DLBCL, PMBCL and FL3B, who have had at least two previous treatments, are due to provide additional evidence within the next 12 months.

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B.4 Cost-comparison analysis

Summary of the cost-comparison analysis

- As described in Section B.1, if recommended, liso-cel is anticipated to displace axi-cel as the current 3L+ SoC for CAR T suitable patients with R/R LBCL; axi-cel represents established clinical practice in this population and both treatments have a similar MoA
- From a MAIC of liso-cel versus axi-cel (see Section B.3.9), liso-cel was found to be associated with comparable efficacy to axi-cel, and a more favourable safety profile
- A cost-comparison analysis was conducted to estimate the cost-savings associated with liso-cel compared with axi-cel. The CCM, developed in Microsoft Excel®, included all relevant costs associated with CAR T-cell therapy administration, as well as additional costs that would be expected to differ substantially between people receiving liso-cel and axi-cel
- Costs included in the CCM were; CAR T treatment acquisition costs, acquisition and administration costs for bridging therapies, a CAR T tariff and resource use costs not explicitly captured within the CAR T tariff (i.e. immunoglobulin replacement therapy and ICU admissions)
- The CCM used the same CAR T tariff for both liso-cel and axi-cel. However, this CAR T tariff was calculated for axi-cel and, therefore, reflects costs associated with axi-cel, not liso-cel, which has a more favourable safety profile. Whilst ICU and immunoglobulin replacement therapy were captured separately, the improved safety profile of liso-cel - not covered in the tariff - could not be captured in the CCM. This uncaptured benefit relates to the lower incidence of AEs associated with liso-cel, enabling potential outpatient delivery and reduced healthcare resource use (HCRU) for the NHS (see Section B.4.2.3). The CCM base case results were therefore likely to be conservative
- Scenario analyses were also conducted using alternative data sources for inputs to explore the impact of the base case CCM inputs and assumptions

Cost-comparison results

- In the base case deterministic analyses, liso-cel (at PAS price) was associated with cost-savings versus axi-cel (at list price), of [redacted] per person
- However, [redacted]
- The DSA results indicated that the model was robust to parameter uncertainty, with none of the parameters resulting in changes in costs greater than £2,000 across any of the analyses
- The results of these scenario analyses demonstrate the robustness of the base case analysis, confirming liso-cel as a cost-saving option versus axi-cel in the patient population of interest
- Overall, the cost-comparison analysis demonstrates that liso-cel will be associated with cost-savings for the NHS as compared with axi-cel, for patients with R/R LBCL who are suitable for CAR T-cell therapy at 3L+

B.4.1 Changes in service provision and management

Relevant comparator

As described in Section B.1, the targeted population for liso-cel is adult patients with R/R LBCL, who are suitable to receive CAR T-cell therapy as a 3L+ treatment. In this population, liso-cel will represent an alternative treatment option to axi-cel, which is considered the most appropriate comparator within this cost-comparison analysis, for the reasons outlined in Section B.1.1, in line with the final NICE scope.[7]

The introduction of liso-cel is not expected to result in any significant increases in healthcare resource use for CAR T suitable patients with R/R LBCL at 3L+. Indeed, as described in the sections below, the introduction of liso-cel is expected to reduce HCRU, and consequently, costs incurred by NHS

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England, when compared to axi-cel. A cost-comparison approach between the two treatments was therefore deemed appropriate for this submission.

CAR T provision

NHS England has established a network of CAR T specialist services, comprising designated treatment centres and a patient care pathway that covers the full lifecycle of CAR T-cell therapy from referral through infusion to follow-up.[154] In clinical practice, the cost of treatment with CAR T-cell therapy is captured by the CAR T tariff. This tariff was calculated from real-world patients treated with CAR T-cell therapy in 2022/23, and predominantly reflects the costs associated with axi-cel. The tariff includes all costs of care from the decision for a person to have CAR T-cell therapy to 100 days after infusion (leukapheresis, in-hospital delivery, in-hospital AEs [excluding ICU admissions and immunoglobulin replacement therapy], 100-day monitoring and training).[6] The most recent value, reflecting 2025/26 financial year, is used in the CCM (£60,462 based on NICE ID6325 for brexu-cel).[113]

The adoption of liso-cel at 3L+ can be readily facilitated in UK clinical practice, and no significant changes in service provision and management will be required, compared to existing CAR T-cell therapies. However, the use of liso-cel at 3L+ may benefit from service provision changes that are currently being introduced from the 2L outpatient pathway. This is not reflected in the CCM, as costs related to the administration of both liso-cel and axi-cel are modelled using the single 2025/26 NHS CAR T tariff cost of £60,462.[113]

AE management

As noted above, AE-related resource use costs were captured by the CAR T tariff (see Section B.4.2.3), with the exception of immunoglobulin replacement therapy and ICU costs. As such, the proportion of patients receiving immunoglobulin replacement therapy (for the treatment of hypogammaglobulinaemia) and the proportion of patients admitted to ICU were included in addition to the CAR T tariff within the CCM for liso-cel and axi-cel. Clinical expert feedback received as part of NICE TA1048 highlighted that the key difference between liso-cel and axi-cel is the safety profile, and that substantially fewer Grade 3 and 4 AEs are expected for people receiving treatment with liso-cel compared with axi-cel.[60] The favourable safety profile of liso-cel is further supported by the results of the MAIC conducted for this submission, which reports a [redacted] in the safety profile of liso-cel compared with axi-cel, with [redacted] (see Section B.3.9). These conclusions are also in line with the results of the original published MAIC.[137] As ICU admissions are typically associated with the management of Grade ≥3 CAR T specific AEs (namely CRS and ICANS), fewer patients are expected to be admitted to ICU following liso-cel treatment as compared with axi-cel.

The improved safety profile of liso-cel also introduces the possibility of outpatient delivery and monitoring. Clinical expert feedback from NICE TA1048 was overwhelmingly in support of the outpatient delivery of liso-cel.[60] This was further reinforced by insights from the TRANSCEND-OUTREACH-007 trial, which indicated that patients with R/R LBCL can successfully be treated and monitored in an outpatient setting (Section B.3.6.4).[110] This is expected to be associated with additional cost-savings compared with axi-cel – which can only be administered in an inpatient setting – given the associated reduction in costs compared with in-hospital administration. Additionally, for sites that are unable to deliver liso-cel in a fully outpatient setting, patients are expected to be discharged earlier than those receiving axi-cel and, therefore, the overall length of hospital stays is anticipated to be reduced following treatment.

The use of a single CAR T tariff inherently assumes that AE-related resource use and costs are equal for liso-cel and axi-cel, which is likely to be conservative given this fails to account for the additional cost savings to the NHS that would result from the more favourable safety profile of liso-cel.[155]

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Additionally, since CAR T delivery costs are included within the CAR T tariff, the use of a single CAR T tariff for both axi-cel and liso-cel results in the CCM failing to capture any of the cost-savings associated with outpatient delivery. As such, the results of the CCM are likely to be conservative, with additional cost savings expected with liso-cel treatment compared to axi-cel.[155]

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Population

The population considered within this CCM was adults with R/R LBCL after two or more systemic therapies (3L+), who are suitable for CAR T-cell therapy, in line with the anticipated use of liso-cel at this place in the pathway. This is in line with the decision problem for this submission, as outlined in Section B.1.1.[1] This population also aligns with the patient population in the TRANSCEND trial, which is the principal evidence base for liso-cel in patients with R/R LBCL at 3L+.[25]

Intervention

The intervention included within the CCM was liso-cel. The clinical efficacy and safety evidence for liso-cel were informed by the DL1+DL2 subtotal of the DLBCL Cohort Efficacy Set and DLBCL Cohort Treated Set of TRANSCEND, respectively. TEAEs and all other inputs in the CCM were based on the TRANSCEND trial, specifically informed by the September 2021 DCO (see Section B.4.2.3).[120, 126]

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.[2] The mechanism of action and process for manufacturing and administering liso-cel is described in Section B.1.2. Following leukapheresis, patients in TRANSCEND were permitted to receive bridging therapy, with [redacted] ([redacted]%) patients in the DL1+DL2 subtotal of the DLBCL Cohort Treated Set receiving bridging therapy at the April 2019 DCO.[126] 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.

Patients were modelled to discontinue treatment following leukapheresis, before receiving LDC and/or CAR T infusion, based on the discontinuation rate reported in the TRANSCEND trial, due to progressed disease, manufacturing failure, patients no longer meeting eligibility criteria, withdrawal of consent or death. As such, patients in the liso-cel arm of the CCM were separated into patients who receive liso-cel infusion and those that did not (Figure 12). In the TRANSCEND trial, as of the September 2021 DCO, [redacted]% of patients in the DL1+DL2 subtotal of the DLBCL Cohort Treated Set underwent leukapheresis but discontinued before starting LDC, and [redacted]% died prior to CAR T infusion, corresponding to a total [redacted]% of patients not receiving LDC or CAR T infusion.[120] These patients were modelled to incur the costs of leukapheresis and, if received, bridging therapy only. Overall, [redacted]% of patients in the DL1+DL2 subtotal of the DLBCL Cohort Treated Set received planned *conforming* liso-cel infusion, who were modelled to incur the full costs of liso-cel infusion. Costs associated with CAR T acquisition for patients who received a non-conforming product were not accounted for ([redacted]% of patients in the DL1+DL2 subtotal of the DLBCL Cohort Treated Set), given this cost will be absorbed by BMS and will not be incurred by the NHS.[120]

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Figure 12: Patient flow within the liso-cel arm of the CCM

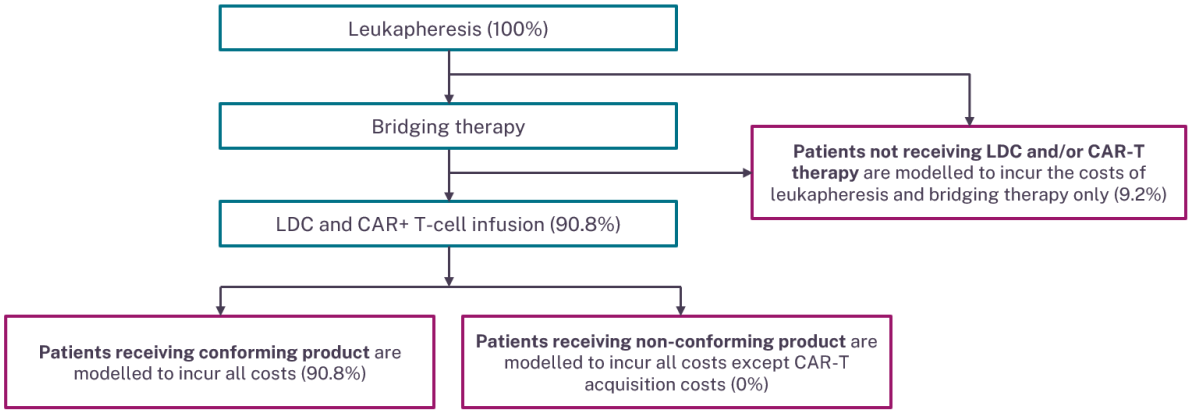
Abbreviations: CAR: chimeric antigen receptor; CCM: cost-comparison model; LDC: lymphodepleting chemotherapy
Source: BMS Data on File (TRANSCEND Clinical Study Report Addendum 01, September 2021);[120] BMS Data on File (TRANSCEND Clinical Study Report, April 2019).[126]

Comparator

As outlined in Section B.1.1, the current SoC in UK clinical practice for patients with R/R LBCL who are suitable for CAR T-cell therapy at 3L+, is axi-cel. As such, axi-cel is considered the most relevant comparator to liso-cel in this submission, in line with the final NICE scope.[7]

In line with the liso-cel arm, patients receiving axi-cel within the CCM were separated into patients who did and did not receive axi-cel infusion, with full costs only being incurred by patients who received axi-cel infusion (conforming product; Figure 13). The ZUMA-1 trial reported that 7.6% of patients underwent leukapheresis but did not commence LDC, and 1.7% of patients died prior to CAR T infusion.[138] This equates to a total of 90.8% of patients receiving planned axi-cel infusion, with no patients modelled to receive non-conforming product.[138]

Figure 13: Patient flow within the axi-cel arm of the CCM



Abbreviations: CAR: chimeric antigen receptor; CCM: cost-comparison model; LDC: lymphodepleting chemotherapy
Source: Locke *et al.* 2019.[138]

Since both the TRANSCEND and ZUMA-1 trials were conducted, there have been large improvements in the manufacturing processes of CAR T-cell therapies in general, due to better patient selection and improved bridging techniques. As such, the difference in the proportion of patients receiving CAR T infusion between the TRANSCEND and ZUMA-1 trials is likely to be the result of the heterogeneity in the two trial designs, rather than a true reflection of UK clinical practice.

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Therefore, the base case analysis assumed an equal proportion of patients infused with either CAR T-cell therapy, informed by patients receiving conforming product in the TRANSCEND trial ([redacted]%; Section B.4.3). An additional scenario was conducted where the proportions of patients receiving liso-cel and axi-cel were directly informed by the TRANSCEND ([redacted]%) and ZUMA-1 (90.8%) trials, respectively (Section B.4.5).

In addition, the proportion of patients receiving bridging therapy differed considerably between TRANSCEND and ZUMA-1, with 0% of patients in ZUMA-1 receiving bridging therapy compared with [redacted]% in TRANSCEND. Feedback from UK CAR T experts confirmed that the ZUMA-1 trial was not reflective of UK clinical practice and that 93.75% of patients would typically receive bridging therapy prior to CAR T infusion.[11] As such, this assumption was used for both liso-cel and axi-cel in the base case analysis (Section B.4.3).

Model structure

A CCM was developed in Microsoft Excel®. The analysis included all relevant costs associated with CAR T-cell therapy administration, as well as additional costs that would be expected to differ substantially between people receiving liso-cel and axi-cel in the target patient population. As such, the CCM included the following costs:

- Treatment acquisition costs for liso-cel and axi-cel
- Acquisition costs for bridging therapies, including treatment combination (R-GemOx [rituximab, gemcitabine and oxaliplatin], Pola-BR [polatuzumab vedotin, bendamustine and rituximab], GDP [gemcitabine, dexamethasone and cisplatin], R-ICE [rituximab, ifosfamide, carboplatin and etoposide] and radiotherapy)
- Administration costs for bridging therapies
- CAR T tariff cost, assumed to include all costs of care from the decision for the person to have CAR T-cell therapy to 100 days after infusion, including drug administration, resource use and AE costs. Only patients who are modelled to receive CAR T infusion incur the CAR T tariff cost (Figure 12)
- Resource use costs not captured within the CAR T tariff (i.e. those associated with immunoglobulin replacement therapy and ICU admissions; Section B.4.2.2)

Subsequent treatment costs were assumed to be equal between patients receiving liso-cel or axi-cel across all treatment years. As the choice of subsequent treatment depends on prior treatment lines, the 4L+ treatments received by patients treated with liso-cel or axi-cel at 3L+ are expected to be closely aligned, as confirmed by UK CAR T Experts.[11] As such, in the 4L+ setting the relative cost between liso-cel and axi-cel is expected to be similar, so these costs were not included within the cost-comparison analysis.

The cost-comparison analysis was conducted in line with the NICE reference case and from an NHS/PSS perspective. Given the one-off nature of CAR T-cell therapies, and assumed similar efficacy between liso-cel and axi-cel, no long-term costs beyond IVIg treatment were modelled and, therefore, no formal time horizon was considered. Discounting was not applied, as recommended by NICE in the user guide applicable to cost-comparison analyses.[155]

B.4.2.2 Intervention and comparator drug acquisition costs

The key inputs, assumptions and acquisition costs included for liso-cel and axi-cel within the CCM are presented in Table 44. Although there are target dose infusions of CAR+ viable T-cells for both liso-cel and axi-cel treatment (100 x 10^6 CAR+ viable T-cells, consisting of CD8 and CD4 components and 2 x 10^6 CAR+ viable T cells/kg of body weight, respectively), the specific infused dose has no bearing on the relative costs of either treatment and, therefore, was not modelled.

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Table 44: Acquisition costs of the intervention and comparator technologies

	Liso-cel	Axi-cel
Pharmaceutical formulation	Each vial contains liso-cel at a batch-specific concentration of autologous T-cells genetically modified to express an anti-CD19 CAR+ T-cells packaged in one or more vials. Each vial contains an extractable volume of 4.6 mL of CD8+ and 4.6 mL of CD4+ cell components.	Each patient-specific infusion bag contains axi-cel at a batch-dependent concentration of autologous T-cells genetically modified to express an anti-CD19 CAR+ T-cells packaged in one infusion bag overall containing approximately 68 mL of dispersion for infusion.
(Anticipated) care setting	Specialist care setting	Specialist care setting
Acquisition cost (excluding VAT)	**List price:** £297,000.00 **PAS price:** £[redacted]	**List price:** £280,451.00[a]
Method of administration	IV	IV
Doses	100 x 10^6 CAR+ viable T cells within a range of 44–122 x 10^6 CAR+ viable T cells	2 x 10^6 CAR+ viable T cells per kg of body weight (within a range of 1–2 x 10^6 cells/kg), with a maximum of 2 x 10^8 CAR+ viable T cells for patients ≥100 kg
Dosing frequency	One-off administration	One-off administration
Dose adjustments[a]	N/A	N/A
Average length of a course of treatment[a]	N/A	N/A
Average cost of a course of treatment (acquisition costs only)	**PAS price:** £[redacted]	**List price:** £280,451.00
(Anticipated) average interval between courses of treatment[a]	N/A	N/A
(Anticipated) number of repeat courses of treatment[a]	N/A	N/A

Footnotes: [a]CAR T-cell therapies are administered as a one-off therapy
Abbreviations: CAR T: chimeric antigen receptor T-cell; IV: intravenous; NA: not applicable; VAT: value added tax.
Source: Liso-cel SmPC;[1] Axi-cel SmPC.[140]

B.4.2.3 Intervention and comparator healthcare resource use and associated costs

An economic SLR was conducted in April 2020 and subsequently updated on 8th June 2020, 5th February 2021, 2nd May 2022, 1st March 2023, 1st February 2024 and 8th September 2025 to identify studies reporting cost and resource use data in R/R LBCL at 3L+. Full details of the methodology and results of the economic SLR are presented in Appendix G. In total, 209 articles reporting on 176 unique studies on cost and resource use data were included in the economic SLR.

CAR T tariff

The CAR T tariff was calculated based on real-world usage of CAR T-cell therapies in 2022/23. The most recent value, reflecting the 2025/26 financial year, is included in the CCM (£60,462). This CAR T

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tariff includes all costs of care from the decision for a person to have CAR T-cell therapy to 100 days after infusion, excluding CAR T acquisition costs, bridging therapy costs, and any costs associated with the treatment of hypogammaglobulinaemia (with IVIg) or ICU costs.[60] The CAR T tariff therefore includes the costs of:

- **Pre-treatment:** Leukapheresis and lymphodepleting chemotherapy
- **Treatment:** All treatment administration costs (excluding those associated with bridging therapy)
- **Post liso-cel infusion:** Resource use and AE management costs up to 100 days after infusion

The CCM allowed patients to discontinue the CAR T pathway following leukapheresis, before receiving LDC and/or CAR T infusion. As such, only patients infused with either liso-cel or axi-cel incur the tariff in the CCM. The proportion of patients who underwent leukapheresis but did not go on to receive CAR T infusion (liso-cel or axi-cel) were also captured in the CCM, and were modelled to incur the costs of leukapheresis and bridging chemotherapy only (Section B.4.2.1, Figure 12).

Bridging therapies

Bridging therapies may be administered between leukapheresis and CAR T cell infusion during the pre-treatment CAR T manufacturing period to maintain disease control, reduce metabolic tumour volume and enhance the success of subsequent CAR T-cell therapy. The regimens received as part of bridging therapy were collected as part of clinician feedback and included R-GemOx Pola-BR, GDP, R-ICE and radiotherapy. The proportion and distribution of patients modelled to receive bridging therapies were based on feedback from UK CAR T Experts, to reflect current clinical practice in the UK, given the rapid evolution of available bridging therapy options. It was estimated that 93.75% of patients receive bridging therapy prior to treatment with CAR T-cell therapies, and the distributions of bridging therapies received were assumed to be the same for patients receiving liso-cel or axi-cel.[11] Given the proportion and distribution of bridging therapies received by patients treated with liso-cel and axi-cel were assumed to be the same, this input does not differentiate cost between the two treatments. As such, these have not been outlined within the submission but are available within the CCM.

Immunoglobulin replacement

Hypogammaglobulinaemia is a common AE event associated with CAR T administration which incidence varies between CAR T treatments. The costs associated with the management of hypogammaglobulinaemia with immunoglobulin replacement therapy are summarised in Table 45. These costs are not included in the CAR T tariff and, so, were accounted for separately within the CCM.[60] Immunoglobulin replacement therapy can be administered intravenously (IVIg) or subcutaneously (SCIg) for the treatment of hypogammaglobulinaemia. Within the CCM, patients are assumed to receive IVIg only, as UK CAR T Experts reported that SCIg administration is only received by a small proportion of patients (20–25%).[11] This proportion varies by centre, with larger centres more likely to administer SCIg due to greater availability of resources and training and is therefore not reflective of general UK clinical practice.[11] As such, immunoglobulin replacement therapy will be referred to as IVIg from here onwards.

As IVIg use was not explicitly captured in the latest DCO of either TRANSCEND or ZUMA-1, the proportion of patients with any grade hypogammaglobulinaemia in both trials were used to model the proportion of patients receiving IVIg in the CCM. Only Grade 1 and 2 hypogammaglobulinaemia were reported in TRANSCEND and ZUMA-1 and both grades were assumed to incur the same management costs, as confirmed by clinician feedback.[11, 120] This approach is considered conservative since IVIg therapy is typically reserved for patients with symptomatic

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hypogammaglobulinaemia (i.e. with infection) who experience recurrent or persistent infections.[11, 156] Additionally, it was assumed that all patients with an individual event of hypogammaglobulinaemia would receive treatment with IVIg since only data for individual events were available. Fewer patients are therefore expected to incur costs of IVIg therapy in UK clinical practice compared with the CCM. However, the effect of these overestimated costs should be negligible, as they apply equally to both arms and effectively offset each other.

It was assumed that IVIgs are administered every four weeks for a duration of 6.5 months across both treatment arms, in line with the approach taken in NICE TA872.[6] Feedback from UK CAR T Experts on the management of hypogammaglobulinaemia confirmed that this was a reasonable approach to modelling the duration of IVIg treatment.[11] Each administration incurred a cost of £665, assumed to equal to the cost of administration of simple parental chemotherapy.

In the base case, the proportion of patients requiring IVIg treatment in both arms was informed by the results of the MAIC of liso-cel versus axi-cel (see Section B.3.9). A scenario was been explored where the proportion of patients requiring IVIg treatment following liso-cel and axi-cel infusion was informed by the data from the TRANSCEND ([redacted]%) and ZUMA-1 (16.00%) trials, respectively (Section B.4.5.1).

Table 45: IVIg related costs used in the base case (MAIC of liso-cel versus axi-cel; TA872; BNF)

Treatment	Proportion of patients requiring IVIg	Duration of IVIg treatment	Cost per unit	Average patient weight	Source
Liso-cel	[redacted]%	6.5 months	£665	78.86 kg	**Proportion**: MAIC **IVIg dosing regimen:** Compagno et al. 2014[157] **IVIg duration:** NICE TA872[6] **Cost:** BNF, Gamunex 10g[158]
Axi-cel	[redacted]%	6.5 months	£665	78.86 kg	**Proportion:** MAIC **Duration/cost/weight**: assumed equal to liso-cel

Abbreviations: BNF: British National Formulary; DCO: data cut-off; IVIg: intravenous immunoglobulin; MAIC: match-adjusted indirect comparison.

ICU admissions

As noted above, since ICU costs are *not* included within the CAR T tariff, these were included separately in the CCM. As a conservative assumption, the CCM includes only the cost of the ICU stay itself, and excludes any additional costs associated with long-term rehabilitation (Table 46).

The costs associated with ICU stays included within the CCM are based on the proportion of patients requiring ICU admission and the duration of ICU stay. The length of ICU stay for patients receiving liso-cel and axi-cel were assumed equal, informed by clinical expert opinion in NICE TA872 (Table 46).[6]

In the base case, the proportion of patients modelled to require ICU admission following liso-cel and axi-cel infusion were based on French 2L RWD (Table 46).[88] This RWD is from a retrospective cohort study of adult patients with R/R LBCL treated with CAR T-cell therapy at 2L in France between 1st January 2018, and 31st December 2024. These patients were identified through the French national hospital discharge databases ("Programme de Médicalisation des Systèmes d'Information" or PMSI),

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which is an exhaustive database for all hospitalisations in France. A total of [redacted] patients with LBCL treated at 2L in 2024 with axi-cel (n=[redacted]) or liso-cel (n=[redacted]) infusion, were included.[88]

Based on this study, the proportion of patients admitted to ICU following liso-cel and axi-cel treatment at 2L in 2024 was [redacted]% and [redacted]%, respectively. Earlier data from this study was accepted to inform ICU admission rates following CAR T-cell therapy in NICE TA1048, based on data collected between 2022–2023 (liso-cel [2L]: 3%; axi-cel [2L]: 13%).[60, 89] This study demonstrated the clear reduction in ICU admissions following liso-cel infusion compared with axi-cel.

Updated data from 2024 demonstrated that a similar proportion of patients were admitted to ICU following axi-cel treatment at 2L ([redacted]%) and 3L ([redacted]% [N=[redacted]]), respectively.[88] This was supported by UK CAR T Experts feedback, who noted that ICU rates for patients receiving CAR T-cell therapies at 2L are similar to those at 3L+, and deemed it appropriate to extrapolate 2L rates to the 3L+ setting.[11] As such, in the absence of ICU data for 3L liso-cel – since it is not currently reimbursed in France – 2L liso-cel data from this RWD study ([redacted]%) informed the proportion of patients admitted to ICU following 3L+ liso-cel in the base case. The proportion of patients admitted to ICU following axi-cel was informed by the same French RWD for patients receiving 3L+ axi-cel ([redacted]%).

A scenario analysis was explored, including ICU admissions for liso-cel ([redacted]%) and axi-cel (16.33%) from the TRANSCEND trial and US RWD (in the absence of data from ZUMA-1), respectively (see Section B.4.5.2).[120, 159] US RWD demonstrated that 16.3% of patients receiving axi-cel who received an early toxicity intervention strategy, based upon ZUMA-1 Cohort 4, consisting of early tocilizumab and corticosteroids were admitted to ICU.[159] Whilst ICU costs were captured, the impact of reduced ICU admissions on patient HRQoL, or the broader substantial impacts that this would have on NHS capacity were not captured in the CCM.

Table 46: ICU related costs used in the base case

Treatment	Proportion requiring ICU stay	Length of stay (days)	Cost per day	Source
Base case (French PMSI study, 2024)				
Liso-cel	[redacted]%	7.5	£6,605.79	**Proportion**: French RWE[59, 88] **LoS:** TA872 Committee Papers[6] **Cost:** NHS Reference Costs 2023/24 Weighted average of SA31 A to F (Elective)[115]
Axi-cel	[redacted]%	7.5	£6,605.79	**Proportion**: French RWE[88] **LoS:** TA872 Committee Papers[6] **Cost:** NHS Reference Costs 2023/24 Weighted average of SA31 A to F (Elective)[115]

Abbreviations: DCO: data cut-off; ICU: intensive care unit; LoS: length of stay; NHS: National Health Service; PMSI: Programme de Médicalisation des Systèmes d'Information; RWE: real-world evidence

B.4.2.4 Adverse reaction unit costs and resource use

As AE unit costs were captured by the CAR T tariff, no additional AE cost savings were considered, beyond ICU and IVIg use, in the CCM. However, since the tariff was calculated from real-world patients treated with CAR T-cell therapy in 2022/23, which was predominantly axi-cel, it reflects costs associated with the safety profile of axi-cel (Section B.2.1). As such, the use of this tariff implicitly assumed equal AE incidences and, therefore, costs associated with liso-cel and axi-cel. Given liso-cel is expected to be associated with a more favourable safety profile compared with axi-cel, as supported by evidence from the MAIC, US RWE and clinical expert opinion (Section B.3.10), the

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assumption of equal AE management costs is likely to be conservative and overlooks additional cost savings for the NHS that resulting from the more favourable safety profile of liso-cel.[11, 13, 14, 136, 155]

B.4.2.5 Miscellaneous unit costs and resource use

All unit costs and resource use are detailed in the sections above; no additional unit costs or resources were considered in the CCM.

B.4.2.6 Clinical expert validation

Individual clinical expert interviews were conducted to validate the clinical assumptions underpinning the CCM.[11] The interviews took place between October to November 2025. There were five UK CAR T Experts interviewed, based in Southampton, Birmingham, Newcastle, London and Nottingham.

The following topics were pre-specified in the interview agendas for four clinicians (Southampton, Birmingham, Newcastle, London):

- Epidemiology estimates
- UK treatment pathway for LBCL, with a particular focus on 3L treatment options and bridging therapies
- Resource use

Additionally, follow-up interviews were held with three of the same clinicians (based in Southampton, Newcastle and London) in November 2025 to capture information on the comparative efficacy between liso-cel and axi-cel.

These four clinicians, who are highly regarded in the CAR T clinical community, were chosen for both their lymphoma and CAR T expertise and to ensure we are capturing variation of practice from across England.

One further clinician (from Nottingham) was interviewed on the management of hypogammaglobulinaemia, particularly in the context of CAR T-cell therapy. The conversation also addressed practical aspects relevant to health economic modelling for therapies such as axi-cel and liso-cel. This clinician was chosen for their leading role in the development of the forthcoming British Society for Haematology guidelines in the management of hypogammaglobulinaemia.

Epidemiology estimates

Clinicians estimated that, on average, 32.71% of patients progress to 2L treatment, and 62.50% of patients progress to 3L treatment, of whom 25.00% are estimated to be suitable for CAR T. Patients not suitable for CAR T-cell therapy at 3L may be attributed to the following:

- Loss of fitness or poor performance status, making them unsuitable for CAR T
- Prior therapies or comorbidities
- Disease characteristics, such as relapse post-CAR T or non-responsiveness
- Patient choice or lack of clinical trial availability
- Symptom management or palliative intent (less than 10%)
- Some centres choose antibody-drug conjugates (e.g., loncastuximab/‘longer’) if unfamiliar with managing bispecific side effects

The UK treatment pathway for LBCL

Clinicians confirmed that approximately 25.00% of patients with R/R LBCL at 3L+ would be expected to be suitable for CAR T-cell therapy.

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Clinicians estimated that approximately 93.75% of patients would be expected to receive bridging therapy prior to any CAR T infusion. The distribution of bridging therapies is approximated as:

- R-GemOX: 13.00%
- Pola-BR: 20.77%
- R-GDP: 14.59%
- R-ICE: 8.19%
- Radiotherapy: 54.70%

It was noted that patients receiving 3L liso-cel or axi-cel would be expected to receive similar treatments at 4L.

Resource use

Clinicians confirmed that ICU admission rates following CAR T-cell therapy infusion are expected to be similar for patients receiving CAR T-cell therapy at 2L or 3L+ and, as such, the extrapolation of 2L ICU data to inform 3L+ estimates is considered appropriate. Additionally, clinicians confirmed that the use of French RWE to inform ICU estimates is considered reflective of UK clinical practice.

Comparative efficacy between liso-cel and axi-cel

Clinicians reviewed three US RWD studies and commented on the generalisability of these cohorts to UK clinical practice.[12-14] They agreed that, despite minor differences in patient characteristics such as age, use of bridging therapy, performance status, and prior transplant rates, the populations in these studies are broadly reflective of typical UK patients with R/R LBCL at 3L+. Notably, the liso-cel cohorts often included older and less fit patients, which was considered representative of UK practice for these patients at 3L+.

Additionally, clinicians stated that both pivotal trials (TRANSCEND for liso-cel and ZUMA-1 for axi-cel) and RWD consistently demonstrate similar efficacy for liso-cel and axi-cel for patients with R/R LBCL at at 3L+. They noted that there was no evidence of inferior efficacy for liso-cel compared to axi-cel, and that they expect UK real-world outcomes to continue to align with those from the US and clinical trials.

Management of hypogammaglobulinaemia

It was noted that in practice, clinicians do not differentiate hypogammaglobulinaemia management strictly by Grade. Therefore, it is reasonable to assume similar management for both Grade 1 and 2. However, it was noted that this a conservative assumption, as in practice not all patients with hypogammaglobulinaemia would receive immunoglobulin replacement therapy.

The duration of IVIg use was estimated as 6.5 months, with no differences anticipated for liso-cel compared with axi-cel, as supported by TRANSCEND and ZUMA-1 trial data.[120, 159]

It was noted that there is significant regional variation in the management of hypogammaglobulinaemia with IVIg or SCIg across England, with the mode of administration influenced by centre size, resources, and local practices. It was estimated that 20–25% of patients would receive SCIg, with the remainder receiving IVIg.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the key model inputs and assumptions and any uncertainties in these is presented in Table 47.

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Table 47: Key model inputs and assumptions

	Base case		Scenario analyses	
	Input and assumptions	**Justification**	**Input**	**Justification**
Proportions of patients infused with CAR T	Not all patients who underwent leukapheresis received CAR T infusion due to manufacturing failure, disease progression or death. Those patients who discontinue for any reason prior to CAR T infusion do not contribute to costs of CAR T-cell therapy. The proportion of patients receiving CAR T infusion were informed by the TRANSCEND trial ([redacted]%) for both liso-cel and axi-cel.	The difference in the proportion of patients receiving CAR T-cell therapy in TRANSCEND versus ZUMA-1 is likely to be the result of the heterogeneity in the two trial designs, rather than a true reflection of UK clinical practice. In addition, since these trials were initiated in 2019 and 2015, respectively, the manufacturing process and patient selection are expected to have since improved and as such, pre-CAR T period outcomes are anticipated to be much improved, with a higher proportion of patients receiving CAR T infusion, in current UK clinical practice. The proportion of patients receiving liso-cel in TRANSCEND was therefore used for both liso-cel and axi-cel in the base case analysis, as a simplifying assumption which aligns with the cost-comparison approach.	The proportions of patients receiving liso-cel and axi-cel were informed by the TRANSCEND ([redacted]%) and ZUMA-1 (90.8%) trials, respectively.	Although the ZUMA-1 trial is unlikely to reflect UK clinical practice, this scenario explores any uncertainty associated with the base case assumption around an equal proportion of patients receive CAR T in either arm.

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	Base case		Scenario analyses	
	Input and assumptions	**Justification**	**Input**	**Justification**
IVIg proportion	The proportion of patients requiring IVIg treatment in both arms was informed by the MAIC-adjusted proportion of patients with hypogammaglobulinaemia reported in the MAIC of liso-cel versus axi-cel. The proportion of patients requiring with hypogammaglobulinaemia were [redacted]% and [redacted]% following liso-cel and axi-cel treatment, respectively.	The alignment of key covariates within the trial populations within the MAIC reduces bias from cross-trial differences and better isolates the individual treatment effects. As such, using the MAIC-adjusted results to inform the IVIg proportions in the CCM generates a more reliable comparison between liso-cel and axi-cel.	The proportion of patients requiring IVIg treatment of hypogammaglobulinaemia following liso-cel and axi-cel infusion were informed by the unadjusted data from the TRANSCEND ([redacted]%) and ZUMA-1 (16.00%) trials, respectively.	This scenario explores any uncertainty associated with the MAIC, by using the unadjusted proportions of patients receiving IVIg in both trials. However, in this analysis, the two patient populations are not matched, and therefore this scenario must be interpreted with caution.
ICU proportion	The proportion of patients modelled to require ICU admission following liso-cel and axi-cel infusion were informed by French RWD (liso-cel [2L]: [redacted]%; axi-cel 3L+]: [redacted]%).[88]	This French RWE study provides comparative data for both liso-cel and axi-cel ICU usage in the same treatment line. This study provided evidence that ICU admissions following axi-cel treatment were comparable between 2L and 3L+, which was further supported by clinical expert feedback. As a similar trend is expected for liso-cel, it was deemed appropriate to extrapolate the 2L ICU admission rates for liso-cel to the 3L+ setting.	Proportion of patients receiving liso-cel or axi-cel requiring ICU stay, informed by the TRANSCEND ([redacted]%) and ZUMA-1 (16.33%) trials.	This scenario explores any uncertainty associated with modelling the proportion of patients requiring ICU admission based on French RWD.

Abbreviations: AE: adverse events; CAR T: chimeric antigen receptor T-cell; ICU: intensive care unit; IVIg: intravenous immunoglobulin; LoS: length of stay; MAIC: matching-adjusted indirect comparison; N/A: not applicable; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSS: personal social services RWE: real-world evidence.

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B.4.3 Base case results

Base case results for the cost-comparison analysis of liso-cel (at PAS price) versus axi-cel (at list price) are presented in Table 48. Liso-cel was associated with cost savings versus axi-cel of [redacted] per patient.

However, [redacted]

Table 48: Deterministic cost-comparison results (liso-cel PAS price; axi-cel list price)

Treatment	Bridging therapy	CAR T tariff costs	CAR T acquisition cost	ICU cost	IVIg cost	Total
Liso-cel	£5,626	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	£5,626	[redacted]	[redacted]	[redacted]	£2,017	[redacted]
Incremental	£0	£0	[redacted]	[redacted]	[redacted]	[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.4.4 Subgroup analysis

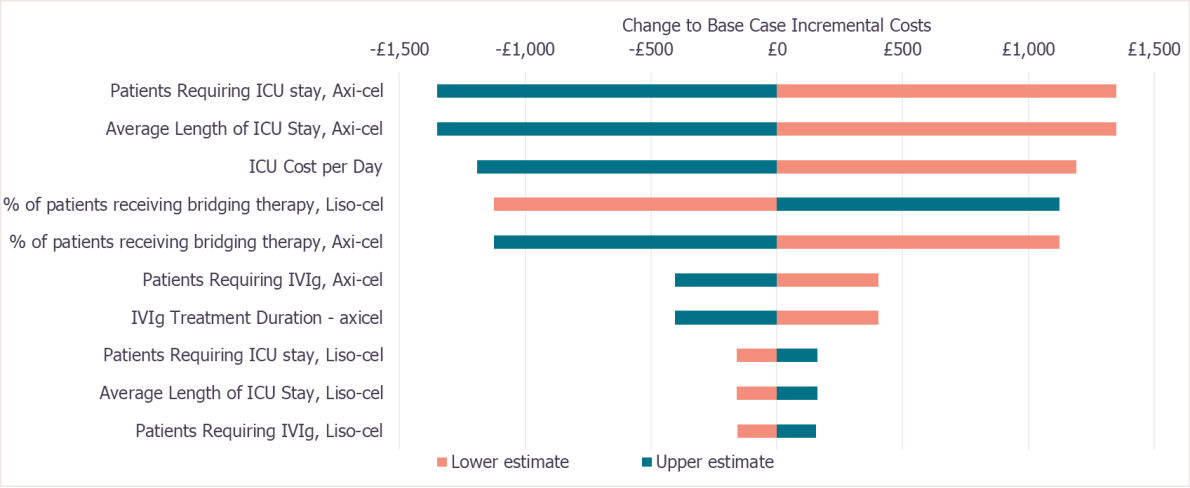
No economic subgroup analyses were conducted for this submission.

B.4.5 Sensitivity and scenario analyses

B.4.5.1 Deterministic sensitivity analysis

To identify key model drivers, a one-way deterministic sensitivity analysis (DSA) was conducted. Parameters were varied one at a time between a +/- 20% variation around the mean. The tornado plot showing the effect of varying parameters is displayed in Figure 14. The number of patients requiring ICU stay following axi-cel infusion, and the length of ICU stay had the largest impact on the incremental cost – although in all cases, the changes were relatively minor (<£2,000).

Figure 14: Tornado plot showing results of the one-way sensitivity analysis



Abbreviations: ICU: intensive care unit; IVIg: intravenous immunoglobulin replacement therapy.

B.4.5.2 Scenario analyses

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Scenario analyses were conducted to explore the impact of the base case cost-comparison analysis model inputs and assumptions, as described in Table 47, with results presented in Table 49. Across all scenario analyses, liso-cel remained cost-saving when compared to axi-cel.

The expectation is that [redacted], liso-cel remains a cost-saving option versus axi-cel across all scenarios.

Table 49: Results of scenario analyses (liso-cel PAS price; axi-cel list price)

#	Model assumption	Base case	Scenario analysis	Incremental costs, £
Base case				[redacted]
1	Proportions of patients infused with CAR T	Equal for liso-cel and axi-cel, informed by TRANSCEND	Informed by TRANSCEND and ZUMA-1	[redacted]
2	IVIg costs (proportion of people experiencing hypogammaglobulinaemia)	Informed by MAIC of liso-cel versus axi-cel	Informed by unadjusted data from the TRANSCEND (liso-cel: [redacted]%) and ZUMA-1 (axi-cel: 16.00%) trials	[redacted]
3	ICU costs (proportion of people requiring ICU stay)	Informed by French RWD (liso-cel [2L]: [redacted]%; axi-cel [3L+]: [redacted]%[88])	Informed by TRANSCEND for liso-cel ([redacted]%) and ZUMA-1 for axi-cel (16.33%)[159]	[redacted]

Abbreviations: ICU: intensive care unit; IVIg: intravenous immunoglobulin; LoS: length of stay; MAIC: matching-adjusted indirect comparison; RWD: real-world data; UK: United Kingdom.

B.4.6 Interpretation and conclusions of economic evidence

The TRANSCEND trial investigated the efficacy of liso-cel in patients with R/R LBCL at 3L+ and demonstrated that treatment with liso-cel resulted in a rapid, high rate of durable CR with long-term survival among a broad range of patients. Axi-cel represents the most relevant comparator to liso-cel in UK clinical practice in the proposed target population, and a MAIC of liso-cel versus axi-cel has demonstrated that liso-cel provides improved health benefit when compared to axi-cel in this patient population due to an improved safety profile (see Section B.3.9). This is supported by RWD and UK CAR T Experts' feedback. The use of a single CAR T tariff assumes that AE-related resource use and costs are the same for liso-cel and axi-cel, and means the additional benefits associated with liso-cel cannot be captured in the CCM. This uncaptured benefit relates to the lower incidence of AEs associated with liso-cel, enabling potential outpatient delivery and reduced healthcare resource use (HCRU) for the NHS. As such, these uncaptured benefits are expected to result in additional cost-savings for the NHS.

In the base case deterministic analyses, liso-cel at PAS price was shown to represent a cost-saving treatment option when compared to axi-cel at list price. Thus, liso-cel can be considered a cost-effective use of NHS resources for patients with R/R LBCL at 3L+. As the results of this analysis are underpinned by the same CAR T tariff for both liso-cel and axi-cel, they are likely to be conservative.

The DSA results indicated that the model was robust to parameter uncertainty, with none of the parameters resulting in changes in costs greater than £2,000 across any of the analyses. The results of these scenario analyses demonstrate the robustness of the base case analysis, confirming liso-cel as a cost-saving option versus axi-cel in the patient population of interest.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments [ID6619]

Summary of Information for Patients (SIP)

28th November 2025

File name	Version	Contains confidential information	Date
ID6619_Liso-cel in LBCL_SIP_28Nov25_CON	**FINAL**	Yes	28th November 2025

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 National Institute for Health and Care Excellence (NICE) for their treatment to be sold to the National Health Services (NHS) for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: 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 treatment for adults with **large B-cell lymphoma**[a] (LBCL) after two or more **systemic therapies.**

LBCL is a type of blood cancer. There are two 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)
- Primary mediastinal B-cell lymphoma (PMBCL)

Specifically, liso-cel will be used as a **third-line or later therapy** in patients with any of the above types of LBCL for whom the disease has not responded to previous treatment (known as **refractory disease**) or has returned following previous treatment (known as **relapsed disease**), who are suitable for a chimeric antigen reception T-cell (**CAR T) therapy**.

[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) granted **marketing authorisation** for liso-cel as a treatment for adults with refractory or relapsed LBCL after two more lines of **systemic therapy** on the 26th October 2023.[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, Blood Cancer Alliance, Cancer, Leukaemia Care, Lymphoma Action and Myeloma UK.

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.

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 are growing, and the type of **proteins** that the abnormal B-cells are expressing. The two subtypes of LBCL considered in this submission are:

- DLBCL. This is the most common type of LBCL, accounting for around 90% of all LBCL cases in the UK[2]
- PMBCL. This is much less common, accounting for around 2–3% of global NHL cases[3, 4]

These subtypes have been grouped together because the disease characteristics and treatment pathways of each of these LBCL subtypes are broadly similar for patients with relapsed or refractory LBCL**.**

For simplicity and brevity, these two subtypes are referred to together as LBCL hereafter.[5] 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 4,400 new cases of LBCL diagnosed each year.[6, 7] 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.[8]

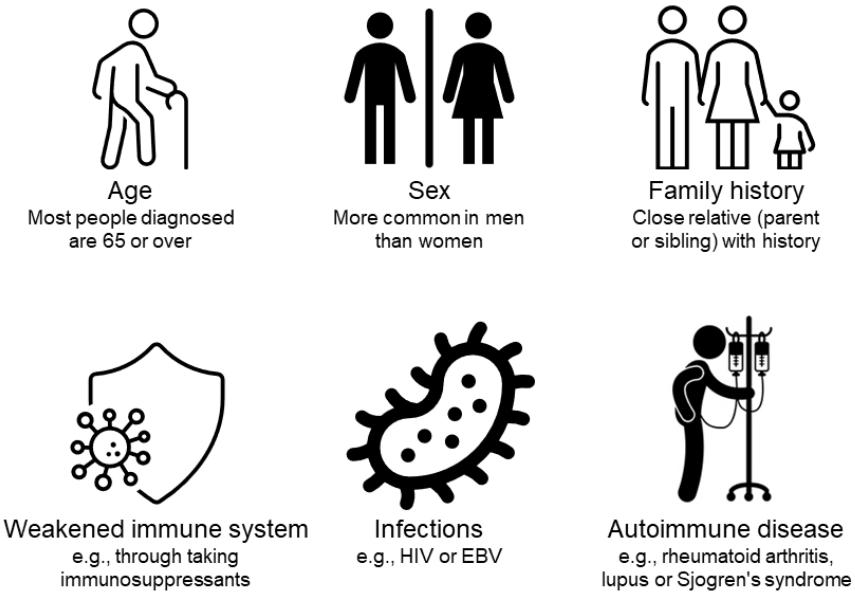
What are the key risk factors for LBCL?

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**).[9, 10]

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).[11] 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.[12-15]

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.[12, 14-16]

Figure 1: Non-modifiable risk factors for LBCL

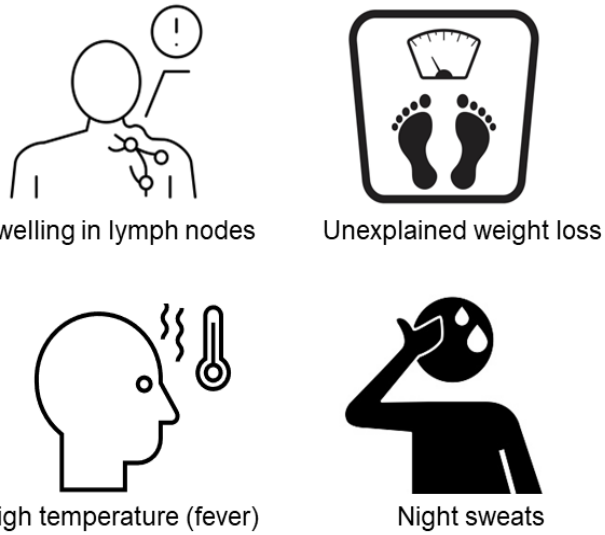


Abbreviations: EBV: Epstein-Barr virus; LBCL: large B-cell lymphoma; HIV: human immunodeficiency virus.

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.[17] 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**.[18]

Figure 2: Initial symptoms of LBCL



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, bowel or brain. When this happens, it is referred to as **extranodal disease**. Symptoms of **extranodal disease** depend on the area affected:[9]

- 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.[19, 20] For patients with refractory/ relapsed LBCL who require subsequent lines of treatment, the potential for a patient to be cured and the expected survival reduces with each line of treatment. Historically at third-line, the life expectancy without **CAR T** therapy was approximately 6 months.[21] The introduction of third-line **CAR T** therapy, however, has dramatically improved life expectancy for patients at third-line to approximately 2 years (24 months).[22]

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 drenching night sweats which may require a change of nightwear and bed covers, a high temperature (fever) with no obvious cause, and unexplained weight loss.[9]

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.[23, 24] 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 relapsed or refractory LBCL face additional challenges. These patients have already endured months of **immunotherapy** and **chemotherapy** with **steroids**. **Immunochemotherapy** can cause various side effects including but not limited to:[25]

- risk of infections
- anaemia
- bruising and bleeding
- **peripheral neuropathy**
- nausea and vomiting
- diarrhoea
- sore mouth and throat
- loss of appetite
- constipation
- tummy pain or indigestion
- tiredness
- hair loss

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:

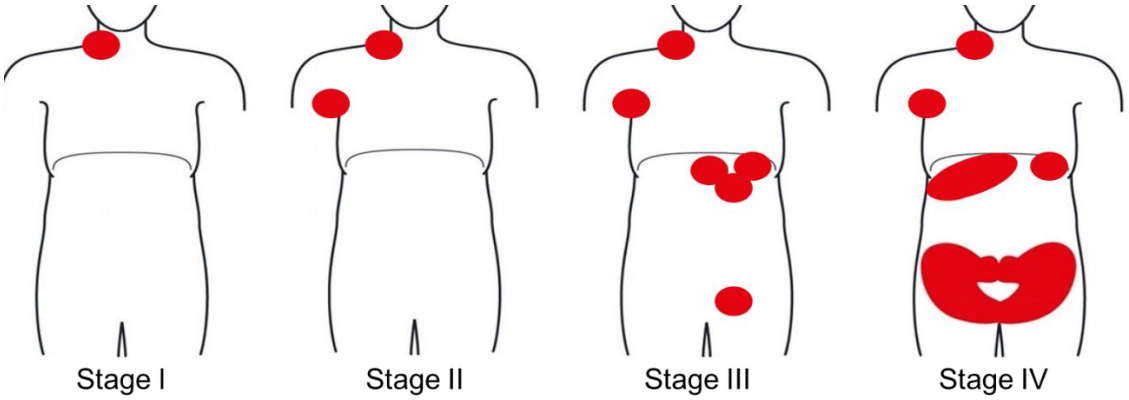
- Low-grade lymphomas are usually slow-growing
- High-grade lymphomas usually fast-growing

LBCL is a high-grade (fast-growing) lymphoma.[9]

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**):[26, 27]

- Stage I: one lymph node or a group of close-by nodes
- Stage II: two or more groups of lymph nodes on the same side of the **diaphragm**
- Stage III: groups of lymph nodes on both sides of the diaphragm
- Stage IV: one or more extranodal organs or tissues

Figure 3: Lymphoma staging system



How is LBCL diagnosed?[28]

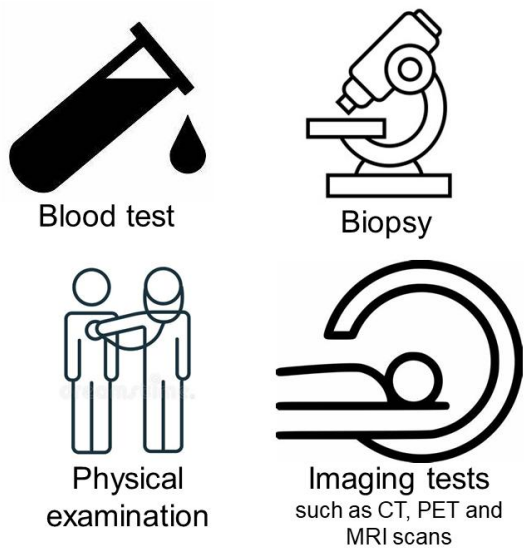
More than a third (36%) of all new NHL cases in the UK are diagnosed in people aged 75 and over and it is more common in men than women.[29] Approximately 60–70% of patients (6–7 in every 10 patients) who are diagnosed with LBCL have advanced stage disease (stage III or IV) at diagnosis.[30]

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 Epstein-Barr virus (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. 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.[9]

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.[5] 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.[9] 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 up to six **cycles** of R-CHOP or Pola + R-CHP over a period of a few months.[9]

A cycle refers to a period of receiving treatment followed by a rest period with no treatment. The specific treatment and number of cycles that a patient receives depends on the type of LBCL and stage of disease..

What is immunochemotherapy?

Immunochemotherapy is a type of treatment is a combination of immunotherapy, chemotherapy and often steroids.

What is immunotherapy?

Immunotherapy 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.

Immunotherapy 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: CAR T therapy, reinduction therapy, high dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) or immunochemotherapy

If first-line treatment for LBCL is unsuccessful or the cancer returns, there are a number of possible second-line treatments available in the UK. Treatment decisions in the second-line setting are determined by the timing of when the cancer returns and whether patients are suitable for **ASCT**, **CAR T** therapy, **bispecific antibody** or no further anticancer treatment.

If a patient's LBCL returns less than 12 months after initial treatment (relapsed) or did not respond to first-line treatment (primary refractory) they can receive **CAR T** therapy (e.g. liso-cel), as their second treatment. **CAR T** therapy is only given if the patient is fit enough to **tolerate** this treatment. More details of the **CAR T** therapy process is provided below.

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 already available in second-line. For this

submission, it is being considered as a potential third-line LBCL treatment. A different **CAR T** therapy, called axi-cel, is available for use in second-line and third-line LBCL by NICE.[31] Axi-cel has been 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 set time period and will need to be reviewed again through the NICE process once this time period has ended.[32]

How does CAR T therapy work?

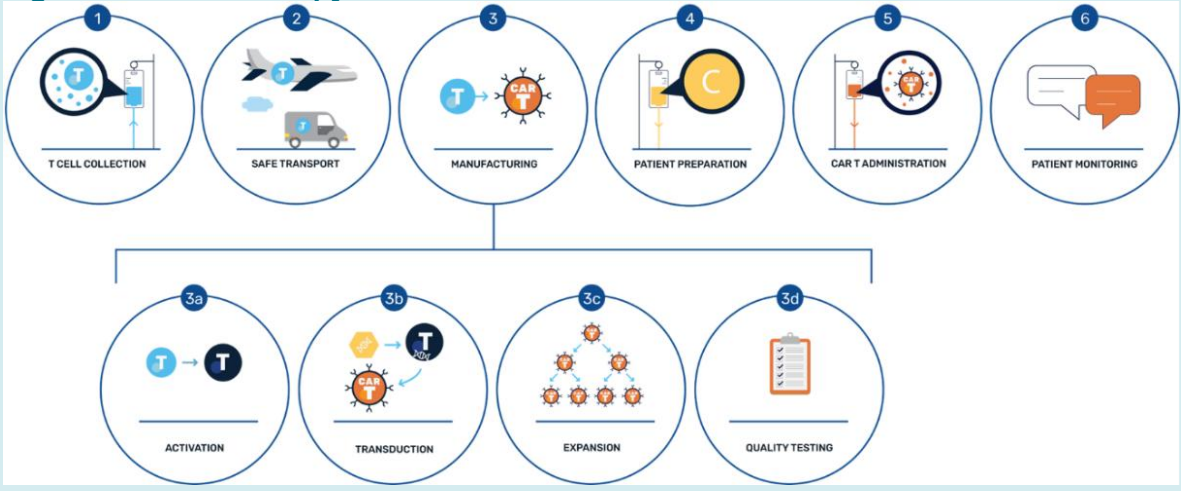
The immune system recognises foreign cells such as cancer cells in the body by identifying **antigens** (proteins) on their surface. T-cells (immune cells) have **receptors** (proteins) that attach to the antigens of foreign cells, which help trigger other parts of the immune system to attack the foreign 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.[33]

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).[33] 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.[33]

Once manufactured, the **CAR T**-cells are then transported back and infused back into the patient through 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[33]



Abbreviations: CAR: chimeric antigen receptor

If a patient's LBCL returns 12 months after initial treatment, they receive a different immunochemotherapy regimen to what they initially received. This immunochemotherapy contains a platinum-based chemotherapy, to try and control the cancer again. This is referred to as reinduction therapy.

If this reinduction therapy is working and the cancer is responding, the patients healthy stem cells are collected from the blood through a process called apheresis, frozen and stored in a stem cell lab, so they can be put back into the body after **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** so the stem cells are removed first. **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 is a combination of four different types of chemotherapy and stands for:

- Carmustine
- Etoposide
- Cytarabine
- Melphalan

The patient will undergo a 5 days of **HDCT** followed by an **SCT**. The type of SCT received is an **ASCT**.

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.

As already mentioned, 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.

Finally, if a patient is not suitable for **CAR T** therapy and SCT, they can receive a **bispecific** and chemotherapy or a different combination of immunochemotherapy compared to what they received at first-line.

Glofitamab, gemcitabine and oxaliplatin (Glofit GemOx) has recently been approved by NICE and is a **bispecific** chemotherapy combination for people who are not suitable for **CAR T**. Glofit GemOx stands for:

- Glofitamab: this is a **bispecific**
- Gemcitabine: this is a type of chemotherapy
- Oxaliplatin: this another type of chemotherapy

For people who are not suitable for **CAR T**, **HDCT** and **ASCT**, one of the most common second-line immunochemotherapy options is rituximab plus gemcitabine and oxaliplatin (R-GemOx). R-GemOx stands for:

- Rituximab
- Gemcitabine
- Oxaliplatin

This is one of the most common second line immunochemotherapy treatments who are not suitable for a **CAR T** of **HDCT** and **ASCT**. Some patients may be treated with **palliative** care if they cannot receive any active treatment.

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. The choice of third-line treatment is primarily determined by the previous treatments received. The focus of this submission is patients who are suitable to receive **CAR T** therapy in the third-line setting and therefore have not received **CAR T** therapy at second-line. For these patients, almost all will receive **CAR T** therapy.

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 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.[34, 35]

What are monoclonal antibodies?

Monoclonal antibodies are a type of targeted immunotherapy that help to identify and attack cancer cells specifically.

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.[36]

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. Radiotherapy can be given at any line of therapy.

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. One person stated that having lymphoma is like 'playing health snakes and ladders.' She explained 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.[37]

Prior appraisals have conducted interviews of patients with LBCL. Non-**CAR T** therapies 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. Common areas of concern with non-**CAR T** therapies 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".[32]

Currently, the only third-line **CAR T** therapy available is axi-cel. While axi-cel is effective for treating LBCL, it can lead to serious side effects such as **cytokine release syndrome (CRS)** and **neurotoxicity (NT).** These side effects require patients to be admitted into the intensive care unit (ICU) for treatment, which is extremely unpleasant. As discussed in Section 3g) Safety of the medicine and side effects below, the new treatment liso-cel is associated with a reduced frequency of these serious side effects.

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.

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?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

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 given?

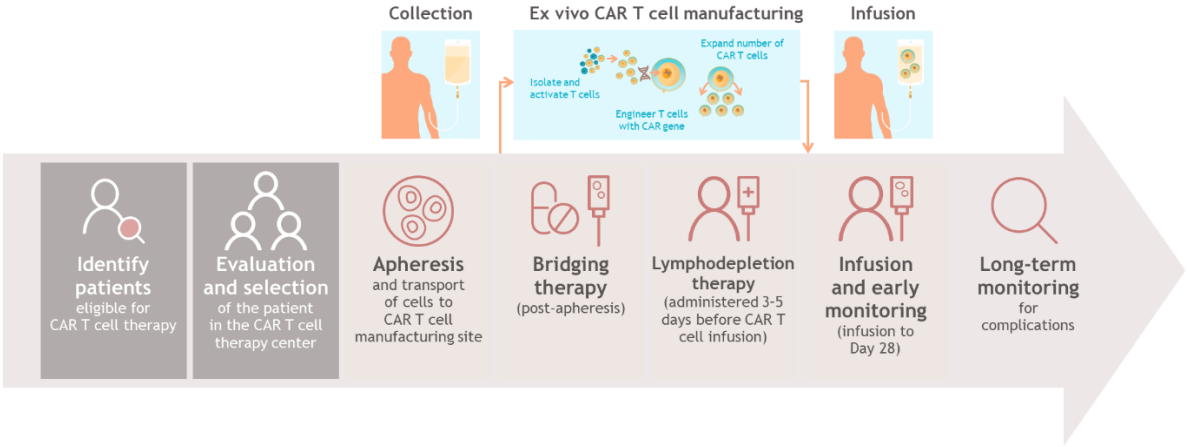
Treatment with liso-cel will be overseen by a healthcare professional who has experience in treating blood cancers and knows how to give liso-cel safely. The healthcare professional will also have training to manage any side effects that might occur.

Liso-cel is delivered frozen to the patients' hospital stem cell lab and is stored until the patient is ready to receive it. The liso-cel infusion is thawed and administered via an intravenous drip (infusion). This whole process of thawing and administering the liso-cel

takes a maximum of 2 hours. The doctors and nurses monitor patients closely during and after the treatment (see **Figure 6).**[38]

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.

Figure 6: CAR T therapy administration and monitoring[33]



Abbreviations: CAR: chimeric antigen receptor

Post-infusion monitoring

After infusion with the **CAR T** therapy, patients are monitored closely for complications that may arise post **CAR T** therapy infusion. Patients receiving axi-cel are required to stay in or close to the hospital for up to 4 weeksost-infusion to monitor for adverse events.[31] Due to the lower risk of adverse events associated with liso-cel compared with axi-cel (see **Section 3g)** Safety of the medicine and side effects, patients receiving liso-cel may not be required to stay in hospital for post-infusion monitoring. Instead, this monitoring can be done in the **outpatient setting**.

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 trials of liso-cel in third-line LBCL

Four clinical trials provide evidence for the safety and efficacy of liso-cel in patients with relapsed or refractory liso-cel after two or more systemic treatments:

- **TRANSCEND** – a Phase 1, single arm clinical trial, meaning it was the first time the treatment has been tested in patients and therefore primarily assessed the safety of liso-cel. The trial included 270 patients from US with DLBCL, PMBCL or follicular lymphoma grade 3B (FL3B) who had received at least two previous systemic treatments.
- **GC-LTFU-001** – an ongoing Phase 2/3, single arm clinical trial, meaning it is assessing the efficacy of the treatment in patients. The trial includes 74 patients who had received **CAR T** therapy in other BMS sponsored trials, including the TRANSCEND study. This study therefore provides longer-term efficacy and safety data for patients who have received liso-cel. The study includes patients from across 17 countries, including the UK.
- **TRANSCENDWORLD** – a Phase 2, single arm clinical trial that was designed to determine the efficacy and safety of liso-cel given at a different dose in an international population of adult patients. The study included a total of 46 patients had received two or more prior systemic therapies that were relevant to the population being considered here.
- **TRANSCEND-OUTREACH-007** – a Phase 2 single arm clinical trial was designed to evaluate the efficacy and safety of liso-cel in patients with 3L+ relapsed or refractory LBCL across both **outpatient** and **inpatient** settings. The trial included 82 patients from the US.

The results from the TRANSCEND trial are discussed in more detail below as this trial is considered most relevant to the patient population being considered in this submission.

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

TRANSCEND

The TRANSCEND trial examined how well liso-cel works and how safe it is for treating patients with relapsed or refractory LBCL who had received two or more prior systemic treatments. The trial measured a number of key outcomes:

- **Overall response rate (ORR):** Overall response rate refers to the proportion of patients who achieve either a **complete response** 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.
- **Progression-free survival (PFS):** This refers to the length of time after receiving treatment for a disease that a patient does not experience progression of their 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 progression-free at 3 years means that a patient has not experienced any 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.

How well does liso-cel work?

In terms of ORR, the TRANSCEND trial showed that 72.7% of patients who received liso-cel achieved a complete or partial response. This means approximately 7 out of 10 patients will experience symptom relief and stabilisation of their disease following treatment with liso-cel.

In addition, the TRANSCEND trial demonstrated that half of all patients who achieved a complete or partial response maintained that response for 20.5 months. This means when patients achieved a response after treatment with liso-cel, this response was durable and generally maintained for over a year and a half.

In terms of PFS, the TRANSCEND trial showed that 40.6% of patients who received liso-cel were alive and progression free at 24 months (2 years) after liso-cel infusion. This means at 2 years following liso-cel infusion, 4 out of 10 people's disease had not progressed or got worse.

Finally, in terms of OS, the TRANSCEND trial showed that 50.5% of patients who received liso-cel were still alive 24 months (2 years) after liso-cel infusion. This demonstrates liso-cel has the potential to extend patients' life. The longer-term follow-up data from the GC-LTFU-001 is considered confidential by the company and cannot be reported here.

In the TRANSCEND trial, patients received liso-cel in one of three different doses. Of these, only two of the dosing schedules were relevant to the **marketing authorisation; h**owever, the efficacy results for the two relevant dosing schedules alone are considered confidential by the Company. As such, the key **efficacy** results for the full population from the TRANSCEND and GC-LTFU-001 trial (OS only) are presented in Table 1. More efficacy results can be found in Company Submission, Section B.2.6.

Table 1: Summary of TRANSCEND key efficacy results

Key efficacy results	Liso-cel (n=257)
ORR	
N, (%)	187 (73%)
CR (%)	
N, (%)	136 (53%)
DoR	
Median, months	23.1
% of patients maintaining response at 24 months	49.5%
PFS	
Median, months	23.9
% of patients alive and progression-free at 24-months	40.6%
OS	
Median, months	29.3
% of patients alive at 24-months	50.5%

Abbreviations: CR: complete response; DoR: duration of response; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; PFS: progression-free survival; OS: overall survival
Source: Abramson et al. 2024[39]

Comparative efficacy

As TRANSCEND was a single-arm trial**,** an alternative statistical approach was used to compare the efficacy of liso-cel with axi-cel. Axi-cel is a different **CAR T** therapy, that is also recommended for use in third and later line LBCL by NICE.[31]

The statistical approach used was called an **indirect treatment comparison** (**ITC**), specifically, an unanchored **matching adjusted indirect comparison** (**MAIC**). The **ITC** is referred to as unanchored because the TRANSCEND study was a single arm trial and therefore there is no common comparator between liso-cel and axi-cel. If there was a common comparator, it would be referred to as an anchored **ITC**.

A **MAIC** is a form of **ITC** used to compare two treatments that have not been tested head-to-head. It uses detailed patient data from one study and published summary results from another, then statistically reweights the first study's patients so they resemble the second study's population on key factors (e.g., age, disease severity) before comparing outcomes. The result is an adjusted estimate of relative effectiveness, but uncertainty can be higher and unmeasured differences between studies may still bias the findings.

The exact results of the **MAIC** are considered confidential by the Company and cannot be reported here, but they align with published results from the previous **MAIC** that

demonstrated no significant difference in efficacy between liso-cel and axi-cel, suggesting these two treatments can be considered equal in terms of efficacy.[40]

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 TRANSCEND trial:

1. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items (EORTC QLQ-C30)
2. The EuroQoL 5-Dimensions questionnaire (EQ-5D)

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.[41]

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 29 to Month 24 of the TRANSCEND trial, the results of the EORTC QLQ-C30 questionnaire showed that the mean scores in global health status meaningfully improved over time compared to their baseline scores collected at Day 29.[39]

EQ-5D-5L

The EQ-5D-5L comprises 5 items (dimensions): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response levels (no problems, slight problems, moderate problems, severe problems, extreme problems/unable). It also includes a visual analogue scale (EQ VAS) for overall self-rated health.

Patients will score themselves for each dimension and these scores are then converted to a single summary number between 1 (perfect health) and 0 (dead); scores can also be negative (worse than dead).

The results of the EQ-5D-5L questionnaire also showed that the mean scores in EQ-5D-5L improved over time up to Month 24, compared to baseline scores collected on Day 29.[39]

In summary, the quality of life results from the TRANSCEND trial show that treatment with liso-cel did improved quality of life for patients who received it.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine 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).

The overall safety profile for patients treated with liso-cel in the TRANSCEND trial is reported in Table 1. As expected, there were a high frequency of AEs associated with liso-cel, but no new safety findings were reported and the AEs reported are line with previous trials for **CAR T** therapies.

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 1: TEAEs during TRANSCEND

Treatment emergent Adverse events (TEAEs)	Liso-cel arm (n=270)
Patients experiencing any TEAE, n (%)	268 (99)
Patients experiencing any serious TEAE, n (%)	122 (45)
Deaths due to TEAEs, n (%)	7 (3)

Abbreviations: Liso-cel: lisocabtagene maraleucel; TEAE: treatment emergent adverse event.
Source: Abramson et al. (2024).[39]

CAR T specific AEs

CAR T is known to be associated with specific AEs called **cytokine release syndrome** (CRS) and **neurotoxicity** (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** therapy specific AEs experienced by patients who received liso-cel in the TRANSCEND clinical trial are presented in Table 2. Both AEs are graded on a scale from 1 to 5, with higher numbers indicating more serious conditions or death from the AEs.

Table 2: CAR T specific AEs occurring after initiation of liso-cel during TRANSCEND

CAR T specific AEs	Liso-cel arm (n=270)
Patients with CRS, n (%)	
Any grade	113 (42)
Grade 1	65 (24)
Grade 2	42 (16)
Grade 3	4 (1)
Grade 4	2 (1)
Grade 5	0
Time to onset, days, median (range)	5 (1–14)

Time to resolution, days, median (range)	5 (1–17)
Patients with NE, n (%)	
Any grade	80 (30)
Grade 1	26 (10)
Grade 2	27 (10)
Grade 3	23 (9)
Grade 4	4 (1)
Grade 5	0
Time to onset, days, median (range)	9 (1–66)
Time to resolution, days, median (range)	11 (1–86)

Abbreviations: AE: adverse event: CRS: cytokine release syndrome; NE: neurological events.
Source: Abramson et al. (2024).[39]

Comparative safety

In addition to a **MAIC** to compare efficacy between liso-cel and axi-cel, a separate **MAIC** was also conducted to compare the safety of liso-cel and axi-cel.

The exact results of the **MAIC** are considered confidential by the Company and cannot be reported here but, overall, the results aligned with those published in a previous **MAIC** which demonstrated that liso-cel is associated with statistically significantly lower odds of adverse events associated with **CAR T** therapy (referred to adverse events of special interest or AESI) compared with axi-cel.[40]

These AESIs include CRS and neurotoxicity, and often require patients to be admitted into the ICU for treatment. A real-world evidence study comparing the ICU admission rates between patients treated with liso-cel and patients treated with axi-cel found the lower odds of adverse events associated with liso-cel translates to fewer ICU admissions for patients treated with liso-cel compared to patients treated with axi-cel in clinical practice.[42] This evidence demonstrates the more favourable safety profile of liso-cel compared with axi-cel and means patients treated with liso-cel are less likely to be admitted to ICU.

The favourable safety profile for liso-cel compared with axi-cel also leads to patients being treated with liso-cel in hospital and sent home the same day. This process, called **outpatient delivery**, prevents the needs for patients to stay in hospital overnight. More details are provided in Section 3h) Summary of key benefits of treatment for patients.

Managing side effects

In the TRANSCEND trial, patients were monitored very closely during the 14 days following liso-cel infusion, at the qualified treatment centre, for signs and symptoms of CRS or NT. Frequency of monitoring after the first two weeks 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 relapsed or refractory LBCL after two or more systemic treatments are as follows:

- **More tolerable treatment**: Axi-cel is associated with a challenging toxicity profile, and patients may require ICU stays to treat and monitor adverse events associated with axi-cel, particularly neurotoxicity and CRS. In ICU, patients experience muscle wasting as they are unable to move and are receiving high-dose steroids, which can worse this effect. Post-ICU, patients can require up to 3 weeks of rehabilitation to recover from the effects of treating these adverse events in ICU. Recovery following ICU is considered the most difficult part of treating patients who have received axi-cel. Patients can experience physical and neurological effects such as anxiety and depression. Real-world evidence from a study conducted in France has demonstrated ICU usage is lower for patients treated with liso-cel compared with axi-cel.[42] The improved safety profile associated with liso-cel compared with axi-cel means fewer patients will requiring ICU admission and experiencing the substantial negative impact this has on quality of life
- **Potential for outpatient delivery:** Axi-cel requires **inpatient** administration for up to 17 days,[31] meaning patients must stay overnight in hospital to be monitored after having received the treatment. Overnight stays in hospital can substantially reduce patient quality of life as patients are less active, are exposed to hospital acquired infections, are able to see their families less frequently and have less freedom in what they eat. Patients have even described feeling like a “caged animal”, when citing the prolonged hospital admission and monitoring required for **CAR T** therapy.[43] Liso-cel can be administered in the outpatient setting and patients do not have to stay in-hospital for monitoring due to its manageable safety profile. Outpatient and inpatient administration have been shown to lead to a similar treatment effect.[44] This option of outpatient delivery therefore provides the same treatment effect as inpatient delivery with the added advantage of removing the need for overnight stays in hospital, substantially improving patient quality of life by sparing patients the physical and emotional distresses associated with hospital stays
- **Disease control:** Liso-cel demonstrated high response rates in TRANSCEND, meaning it is effective at shrinking tumours and reducing the spread of the disease.

Indirect treatment comparisons have demonstrated liso-cel is similar to axi-cel at reducing the spread of disease and extending patient survival.

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. However, as highlighted in Section 3g) the frequency of serious side effects is expected to be lower with liso-cel compared with axi-cel.

As mentioned above in Section 3g, 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 axi-cel.

How the model reflects the condition

The economic model for this submission was designed to reflect the key features of relapsed or refractory LBCL after two or more previous systemic treatments.

The main treatment that liso-cel was compared to, referred to as the 'comparator', was axi-cel. Given the results of the comparative efficacy described above, it was assumed the efficacy between liso-cel and axi-cel is equal in the model, and therefore the model was designed to compare the costs associated with the two treatments.

To do this, a model structure called a **cost-comparison model** was developed.

- The goal of the model was to compare the costs associated with patients treated with liso-cel compared to axi-cel
- The model assigned patients to the two different treatments (liso-cel or axi-cel) and added together the costs over the patients' lifetimes depending on which of the treatment they might receive in the real world
- Liso-cel and axi-cel have been demonstrated to be equally effective (see Section 3c). This means if liso-cel is cheaper or similar to axi-cel in terms of the money it costs, liso-cel is considered a "good use of NHS resources"

Modelling how the costs of current treatment differ with liso-cel

Various different costs were included in the model for both liso-cel and axi-cel. These costs included:

- The cost of pre-treatment with **leukapheresis**, **bridging therapy** and **lymphodepleting** chemotherapy
- The cost of each **CAR T** therapy and how much they costs to administer the medicine
- The cost of side effects that happen during treatment

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in **Document B, Section B 4.2.7**. The main assumptions used

in the model form 'the base case' which BMS 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 proportion of patients who are actually infused with liso-cel or axi-cel after being deemed suitable for **CAR T** therapy; this was assumed to be equal between both treatments. Data from the respective clinical trials for each treatment showed liso-cel was infused in a lower proportion of patients compared to axi-cel. However, this difference was considered to be the result of the differences in the patient populations in the two trial designs, rather than a true reflection of UK clinical practice. Analyses were conducted to test the uncertainty around this assumption which demonstrated consistent cost savings between liso-cel and axi-cel when using different inputs for each treatment based on data from the clinical trials.

Variations of other inputs and assumptions in the model were also tested and the results of these tests are explained in **Document B, Section 4.5**

Cost comparison results

Based on the modelling inputs and assumptions from BMS, treatment with liso-cel was shown to be a cost-saving treatment option when compared with axi-cel. This is because liso-cel offers a cheaper treatment option taking into account its acquisition cost and the reduced ICU usage compared with axi-cel. Liso-cel therefore represents 'value for money' to the NHS because it is providing equivalent improvements in health whilst offering a safer option for patients with LBCL which translates into a cheaper treatment overall compared to medicines already available.

Benefits of liso-cel not captured in the economic analysis

There are likely to be additional cost savings associated with liso-cel that could not be captured in the economic model. This is because NHS England has calculated a **CAR T** tariff that is intended to reflect the costs associated from the point of decision for a person to have **CAR T** therapy to 100 days after infusion. The only costs not captured in the **CAR T** tariff are the cost of any drugs (e.g. liso-cel, axi-cel and bridging therapies) and the cost of managing costly AE (e.g. when a patient is admitted to ICU or requires **antibody** replacement therapy).

This tariff is required to be used in the economic model and assumed to be equal between liso-cel and axi-cel. This approach therefore assumes resource use and costs associated with managing AEs are the same for liso-cel and axi-cel, which means it does not account for the expected cost-savings from liso-cel's improved safety profile. Furthermore, the economic analysis does not capture the benefits associated with delivery in the outpatient setting with liso-cel compared with axi-cel. Consequently, the additional benefits of liso-cel being a safer option, leading to potential cost savings for the NHS, are not reflected in the economic analysis.

Conclusion

The benefits outlined in Section 3h 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 relapsed or refractory LBCL who have received at least two prior systemic treatments.

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.

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. Liso-cel has a specific **CAR T** design which may contribute to the favourable safety profile of liso-cel compared to other available **CAR T** therapies.[45] Liso-cel is also suitable for administration in the outpatient setting, avoiding the need for patients to stay in hospitals and improving their quality of life.

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

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.

Adverse event	Any unwanted or unexpected sign, symptom, or health problem that happens during medical care or after taking a medicine, vaccine, or having a procedure
Antibody	A protein made by the immune system to help defend against infection
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	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 drenching night sweats 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 or radiotherapy) given to patients whilst they wait to receive other treatments.
CAR T therapy	A special type of immunotherapy that is made from your own immune cells and uses your own immune cells to fight cancer
Chemotherapy	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.
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.
Cost-comparison model	A type of health economic model that only compares the costs of treatments
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 depends on the specific treatment combination and the number of cycles is often dependant on whether the treatment has spread.
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.
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 set of treatment given for your disease or illness.
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 chemotherapy drugs at significantly higher doses than standard doses of 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.
Indirect treatment comparison	A statistical method to compare two treatments when they have not been tested head-to-head in the same clinical trial.
Inpatient	A patient who is admitted to hospital and stays overnight (or longer) to receive care
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	Apheresis that involves the collection of specific white blood cells from the blood. 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 throughout the body. 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.
Matching adjusted indirect comparison	A type of indirect treatment comparison where patient data from one study is adjusted (or “rebalance”) so that the people in that study look more like the people in a different study that included the comparator
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.
Magnetic resonance imaging (MRI)	A type of scan that uses a strong magnet and radio waves to create detailed pictures of the inside of your body without using X-rays
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).
Outpatient	A patient who receives medical care or tests at a hospital or clinic but does not stay overnight.

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.
Peripheral neuropathy	Damage to nerves outside of the brain and spinal cord.
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.
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 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 set of 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.
Systemic therapy	A type of cancer therapy usually given in tablet form or through the vein, that is aimed at the whole body or multiple organs, not just at a specific location.
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 therapy	This is the third set 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

Cost Comparison Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments (review of TA987) [ID6619]

Clarification questions

December 2025

File name	Version	Contains confidential information	Date
ID6619_Liso-cel in LBCL_Clarification Questions Response Document_20Jan26_NoCON	1.0	No	20th January 2026

Section A: Clarification on effectiveness data

TRANSCEND study censoring rules and sample sizes

A1. The company submission (CS) mentions in several places (e.g. CS table 10: CS page 61) that [redacted] patients from TRANSCEND enrolled in the GC-LTFU-001 study. However, CS Table 11 states that [redacted] patients who completed TRANSCEND were enrolled in GC-LTFU-001 and this gave a sample size of [redacted] for the long-term DL1 and DL2 efficacy cohort.

a. Please would you explain the discrepancy between [redacted] and [redacted] enrolling in GC-LTFU-001?

The TRANSCEND Clinical Study Report (CSR; data cut-off [DCO]: May 2024; Table 11) reports that [redacted] patients from the total diffuse large B-cell lymphoma (DLBCL) Cohort Treated Set consented to take part in GC-LTFU-001. Of these patients, [redacted] received the dose level 1 or dose level 2 (DL1+DL2) dosing regimen.[1] Table 10 of the company submission (CS) presents data for the DL1+DL2 subgroup of the DLBCL Cohort Treated Set, reporting outcomes for all [redacted] patients receiving the DL1+DL2 dosing regimen. In contrast, Table 11 of the CS presents the number of patients in the total DLBCL Cohort Treated Set who completed the TRANSCEND trial and enrolled in the GC-LTFU-001 study, reporting a total of [redacted] patients.

Bristol Myers Squibb (BMS) notes a typographical error in question A1, part a – please could "discrepancy between [redacted] and [redacted] enrolling" be updated to "discrepancy between [redacted] and [redacted] enrolling". Additionally, BMS requests that '[redacted]' is marked as confidential. An updated CS has been shared alongside this response, with these data marked as confidential.

b. Please would you explain what the sample size of [redacted] is referring to, given that the sample size used for the long-term follow up analysis of overall survival (OS) is consistently reported elsewhere in the CS as 216 (e.g. CS Table 21 and CS Figure 8).

BMS apologises for the typographical error here. The sample sizes for the analysis of OS in the DLBCL Cohort Efficacy Set reported in Table 11 of the CS are incorrect. The correct values for the sample size of patients in the DLBCL Cohort Efficacy Set included in the long-term OS analysis from GC-LTFU-001 are as follows: total N=257 and DL1+DL2 N=216, as reported in Table 8 of the TRANSCEND CSR (DCO: May 2024) and Table 9 and elsewhere throughout the CS.[1-3]

c. Please would you confirm whether the following EAG interpretations are correct: (i) As the survival analysis was applied to all 216 patients in the original TRANSCEND Efficacy Cohort, those patients who did not enter the GC-LTFU-001 study were censored. (ii) The distinct

clustering of censoring in CS Figure 7 (PFS) and CS Figure 8 (OS) primarily reflects censoring of those patients who completed the TRANSCEND study.

Yes, the EAG is correct in that patients in the TRANSCEND DLBCL Cohort Efficacy Set who did not enter the GC-LTFU-001 study were censored for the analysis. The distinct clustering of censoring at 24 months in both Figure 7 (progression-free survival [PFS]) and Figure 8 (OS) of the CS reflects the final analysis for TRANSCEND, with 24 months follow-up corresponding to the last patient last visit for the DLBCL Cohort.[1]

A2. According to Table 7 in the November TRANSCEND 2024 clinical study report (CSR), under the FDA censoring rules 16.7% of participants had received new anti-cancer therapy at the 16 May 2024 data cutoff. Please would you clarify which therapy this refers to and at which timepoints this censoring occurred.

A summary of the new anticancer therapies received by patients in the DL1+DL2 subtotal of the DLBCL Cohort Efficacy Set (N=216) is presented in Table 1.[4]

Table 1: Summary of new anticancer therapies (DLBCL Cohort Efficacy Set; DCO: 16th May 2024)

Outcome	DL1+DL2 (N=216)	Mean (Censoring date), Months[a]
Any anticancer therapy[b]	[redacted]	[redacted]
Systemic treatment[c]	[redacted]	[redacted]
Atezolizumab, mosunetuzumab	[redacted]	[redacted]
Mosunetuzumab, atezolizumab, dexamethasone	[redacted]	[redacted]
Mosunetuzumab, atezolizumab	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Fludarabine/cyclophosphamide lymphodepleting therapy followed by axicabtagene ciloleucel (axi-cel)	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Idelalisib	[redacted]	[redacted]
Inv-(2015-1132) KA2237	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Obinutuzumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Pembrolizumab, vorinostat	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Rituximab, high-dose methotrexate, cytarabine	[redacted]	[redacted]
R-lenalidomide[d]	[redacted]	[redacted]
Revlimid	[redacted]	[redacted]

Rituximab, magrolimab	[redacted]	[redacted]
Rituximab, lenalidomide[d]	[redacted]	[redacted]
Rituximab, Revlimid[d]	[redacted]	[redacted]
Radiotherapy[c]	[redacted]	[redacted]

Footnotes: [a] Time from first infusion to new anticancer therapy. Using censoring date from PFS - IRC assessment, FDA censoring rules. [b] Percentage based on the number of subjects in DL1+DL2 Subtotal cohort. [c] Percentage based on the number of subjects who received any new anticancer therapy. [d]Treatment regimens can be reported under different nomenclature (branded or generic).
Abbreviations: axi-cel: axicabtagene ciloleucel; DCO: data cut-off; DL: dose level; DLBCL: diffuse large B-cell lymphoma; FDA: Food and Drug Administration; IRC: Independent Review Committee; PFS: progression-free survival; R-lenalidomide: rituximab, lenalidomide.
Source: BMS Data on File (TRANSCEND Clinical Study Report, May 2024 – Supplementary Table).[4]

MAIC interpretation – study selection

A3. Ninety unique studies were included in the clinical SLR (Figure 1 of the 2025 Clinical SLR report) and we note that several studies of the axi-cel comparator treatment are in the included studies list of the February 2021 update search (Appendix B of the 2021 Clinical SLR Suppl appendices document). However, the specific reasons for excluding these axi-cel studies from consideration for the MAIC are not clear. Please would you provide a list of all the axi-cel studies identified over all iterations of the SLR with a specific reason for excluding each of them from the MAIC.

A total of 191 publications (90 unique studies) were included in the clinical systematic literature review (SLR). Of the 42 axicabtagene ciloleucel (axi-cel) publications included, 38 were excluded from the matching-adjusted indirect comparison (MAIC). A summary of the axi-cel publications included in the clinical SLRs are presented in Table 1. For each included publication, a rationale for exclusion from the MAIC is reported. The majority of publications were excluded from consideration in the MAIC due to incomplete or insufficient data. For example, many publications were conference abstracts or only reported subgroup analyses. Some were excluded as they presented data for ZUMA-1 from the same or earlier data cuts as publications that were already included in the MAIC.

As summarised in Section 3.2 of the company MAIC report, the original indirect treatment comparison (ITC) was conducted based on the most comprehensive data source at the time, Locke *et al.* 2019, and its supplementary materials, including the ZUMA-1 statistical analysis plan and study protocol.[5, 6] The Food and Drug Administration (FDA) and European Medicines Agency (EMA) assessment reports for axi-cel were consulted when additional clarity on study design and variable/outcome definition was needed (see Table 26 of the CS). To support the current NICE submission, the MAIC was updated using the most recent available data source for both lisocabtagene maraleucel (liso-cel; DCO: 16 May 2024) and axi-cel (DCO: 11 August 2021).[7] Since the most recent ZUMA-1 publication, Neelapu *et al.* 2023, reported updated data for PFS and OS (DCO: 11 Aug 2021), the updated MAICs for PFS and OS used this publication as the data source for axi-cel.[8]

Table 2: Axi-cel publications identified in the clinical SLR

SLR update	Reference	Reason for exclusion	Rationale
Original SLR April 2019	Neelapu SS, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. 2-year follow-up and high-risk subset analysis of ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma [abstract]. Blood. 2018 Dec 1-4; 132 Suppl 1: Abstract 2967.	Incomplete / insufficient / partial data	A more recent publication with longer-term follow-up (5-year) for ZUMA-1 was available (PFS, OS). This is the abstract for the original publication. Data for the MAIC was obtained from the 5-year follow-up instead as it is more comprehensive and detailed.
	Neelapu SS, Locke FL, Bartlett NL, Lekakis L, Miklos D, Jacobson CA, et al. Kte-C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large b-cell lymphoma (DLBCL): results from the pivotal phase 2 ZUMA-1 [abstract]. Blood. 2016 128(22): Abstract 998.	Incomplete / insufficient / partial data	A more recent publication with longer-term follow-up (5-year) for ZUMA-1 was available. Additionally, this publication did not include Kaplan-Meier (KM) curves and did not report all outcomes of interest.
	Yescarta FDA prescribing information.	-	This study was included. Please refer to Section 3.2 of the company MAIC report for more information.[7]
	Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31-42.	-	This study was included. Please refer to Section 3.2 of the company MAIC report for more information.[7]
February 2021 SLR Update	Diakite I, Lin VW, Klijn S, Navale L, Purdum AG, Fenwick E, et al. Two-year survival with axicabtagene ciloleucel in relapsed or refractory large b-cell lymphoma: An updated analysis [abstract]. HemaSphere. 2019a 3 Suppl 1: 817: Abstract PB1782.	Study design	This abstract does not report KM curves or outcomes/characteristics of interest, as it is a modelling study.
	Neelapu SS. An interim analysis of the ZUMA-1 study of KTE-C19 in refractory, aggressive non-Hodgkin lymphoma. Clin Adv Hematol Oncol. 2019b Feb 15;15(2):117-20.	Study design	This is a commentary article, not an original research paper. It does not report KM curves, or all outcomes or characteristics of interest.
	S. S. Neelapu, A. Ghobadi, C. A. Jacobson, D. B. Miklos, L. J. Lekakis, O. O. Oluwole, Y. Lin, I. Braunschweig, B. T. Hill, J. M. Timmerman, A. Deol, P.	Other: Outdated data	This is a supplement to the full original publication that was used for the analysis. Longer-term follow-

	M. Reagan, P. Stiff, I. W. Flinn, U. Farooq, A. Goy, P. A. McSweeney, J. Munoz, T. Siddiqi, J. C. Chavez, A. F. Herrera, A. Xue, Y. Jiang, A. Bot, J. M. Rossi, J. J. Kim, W. Y. Go, F. L. Locke. "Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: Long-term safety and efficacy of ZUMA-1". British Journal of Haematology (2019). 185 (Supplement 1): 26-27.		up (5-year) for PFS and OS from ZUMA-1 was available from more recent publication.
	S. S. Neelapu, C. A. Jacobson, O. O. Oluwole, J. Munoz, A. Deol, D. B. Miklos, N. L. Bartlett, I. Braunschweig, Y. Jiang, J. J. Kim, L. Zheng, J. M. Rossi, F. L. Locke. "Outcomes of patients (pts) >= 65 years of age in ZUMA-1, a pivotal phase 1/2 study of axicabtagene ciloleucel (axi-cel) in refractory large B-cell lymphoma (LBCL)". Journal of Clinical Oncology. Conference (2019). 37(Supplement 15).	Incomplete / insufficient / partial data	This publication only provided subgroup analyses of patients aged ≥65 years from ZUMA-1.
	S. S. Neelapu, F. L. Locke, N. L. Bartlett, L. J. Lekakis, D. B. Miklos, E. D. Jacobsen, I. Braunschweig, O. O. Oluwole, T. Siddiqi, Y. Lin, J. M. Timmerman, P. M. Reagan, A. Bot, J. M. Rossi, L. Navale, Y. Jiang, J. S. Aycock, M. Elias, J. S. Wiezorek, W. Y. Go. "Long-term follow-up zuma-1: A pivotal trial of axicabtagene ciloleucel (AXI-CEL; KTE-C19) in patients with refractory aggressive non-hodgkin lymphoma (NHL)". Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH (2017). 130(Supplement 1).	Incomplete / insufficient / partial data	A more recent DCO was available elsewhere. No KM curves and not all outcomes or characteristics were reported.
	Diakite I, Lin VW, Klijn S, Navale L, Purdum AG, Fenwick E, et al. An updated two-year survival analysis of axicabtagene ciloleucel (axi-cel) in relapsed or refractory large B-cell lymphoma (R/R-LBCL) [abstract]. Value in Health. 2019b 22 Suppl 2: S41: Abstract MS2.	Study design	This abstract does not report KM curves or outcomes/characteristics of interest, as it is a modelling study.
	Strati P, Adkins S, Nastoupil L, Westin J, Hagemeister F, Fowler N, et al. Clinical implications of cytopenias beyond day 30 after AXI-cel therapy in patients with relapsed/refractory large B-cell lymphoma [abstract].	Incomplete / insufficient / partial data	This is a subgroup analysis of those with available complete blood counts for cytopenia outcomes only.

	Hematological Oncology. 2019 37; Suppl 2: 311-312: Abstract 256.		
	Neelapu S, Locke F, Bartlett N, Lekakis L, Reagan P, Miklos D, et al. A comparison of two-year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory large B cell lymphoma [abstract]. Blood. 2019a Dec 7-10; 134 Suppl 1: Abstract 4095.	Other: Outdated data	More recent data was available (OS). Not all outcomes and characteristics of interest reported. Had the same DCO as the more detailed full publication used.
	Yescarta (EMA Public Assessment Report). Assessment Report. 2018 Contract No.: Procedure No. EMEA/H/C/004480/0000.	-	This study was included. Please refer to Section 3.2 of the company MAIC report for more information.[7]
	Yescarta (Summary of Product Characteristics). Amsterdam, The Netherlands: Kite Pharma EU B.V; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf.	-	This study was included. Please refer to Section 3.2 of the company MAIC report for more information.[7]
	Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017b Dec 28;377(26):2531-44.	Other: Outdated data	A more recent DCO was available.
	Topp MS, Van Meerten T, Wermke M, Lugtenburg EJ, Minnema MC, Song KW, et al. Preliminary results of earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL) [abstract]. J Clin Oncol. 2019a 37; Suppl 15: Abstract 7558.	Incomplete / insufficient / partial data	More recent data was available, and outcomes were only available for a non-randomised safety expansion cohort that evaluated early steroid use.
	Topp MS, Van Meerten T, Wermke M, Lugtenburg EJ, Minnema MC, Song KW, et al. Earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B cell lymphoma [abstract]. Blood. 2019b 134; Suppl 1: Abstract 243.	Incomplete / insufficient / partial data	This publication only reports outcomes for the non-randomised safety expansion cohort. Not all outcomes/KM curves and baseline characteristics of interest were reported.
	Bennani NN, Maurer MJ, Nastoupil LJ, Jain MD, Chavez JC, Cashen AF, et al. Experience with axicabtagene ciloleucel (axi-cel) in patients with secondary CNS involvement: results from the US	Incomplete / insufficient / partial data	This is a subgroup analysis of those with history of secondary central nervous system (CNS) involvement or had active CNS disease at time of infusion.

	Lymphoma CAR T Consortium [abstract]. Blood. 2019 Dec 7-10;134 Suppl 1: Abstract 763.		
	Jain MD, Jacobs MT, Nastoupil LJ, Spiegel JY, Feng G, Lin Y, et al. Characteristics and outcomes of patients receiving bridging therapy while awaiting manufacture of standard of care axicabtagene ciloleucel CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium [abstract]. Blood. 2019 Dec 7-10; 134 Suppl 1: Abstract 245.	Incomplete / insufficient / partial data	This is an analysis of those that received bridging therapy (exclusion in ZUMA-1) compared to those that did not. This did not report all outcomes or baseline characteristics of interest.
	Kuhnl A, Roddie C, Martinez-Cibrian N, Menne TF, Linton K, Lugthart S, et al. Real-world data of high-grade lymphoma patients treated with CD19 CAR-T in England [abstract]. Blood. 2019 Dec 7-10; 134 Suppl 1: Abstract 767.	Incomplete / insufficient / partial data	More recent and longer-term follow-up data was available (OS). Not all outcomes and characteristics of interest were reported.
	Novo M, Sidiqi M, Paludo J, Gandhi S, Kubusek J, Truong T, et al. Peak lymphocyte count after CAR T infusion is a clinically accessible test that correlates with clinical response in axicabtagene ciloleucel therapy for lymphoma [abstract]. Blood. 2019 Dec 7-10; 134 Suppl 1: Abstract 4106.	Incomplete / insufficient / partial data	Not all outcomes and baseline characteristics of interest were reported.
	Riedell PA, Walling C, Nastoupil LJ, Pennisi M, Maziarz RT, McGuirk JP, et al. A multicenter retrospective analysis of clinical outcomes, toxicities, and patterns of use in institutions utilizing commercial axicabtagene ciloleucel and tisagenlecleucel for relapsed/refractory aggressive B-cell lymphomas [abstract]. Blood. 2019 Dec 7-10;134 Suppl 1: Abstract 1599.	Incomplete / insufficient / partial data	Not all outcomes and baseline characteristics of interest were reported.
	Thieblemont C, Le Gouill S, Di Blasi R, Cartron G, Morschhauser F, Bachy E, et al. Real-world results on CD19 CAR Tcell for 60 French patients with relapsed/refractory diffuse large B-cell lymphoma included in a temporary authorization for use program [abstract]. Hematol Oncol. 2019 June; 37 Suppl 2: 301: Abstract 246.	Study design	This is a descriptive analysis of patients included in a cohort patient program allowed to use CD19 chimeric antigen receptor (CAR) T-cells and did not report efficacy outcomes.

	Locke, F. L., Neelapu, S. S., Bartlett, N. L., Siddiqi, T., Chavez, J. C., Hosing, C. M., Cashen, A., Budde, L. E., Sherman, M., Rossi, J. M., Navale, L., Jiang, Y., Aycock, J., Elias, M., Wiezorek, J., Go, W. Y.. "Ongoing complete remissions in phase 1 of ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma (NHL)". Annals of Oncology (2016). 27(Supplement 6): vi359.	Incomplete / insufficient / partial data	This publication only provided subgroup analyses of patients with NHL from ZUMA-1.
	Neelapu, S. S., Jacobson, C. A., Oluwole, O. O., Munoz, J., Deol, A., Miklos, D. B., Bartlett, N. L., Braunschweig, I., Jiang, Y., Kim, J. J., Zheng, L., Rossi, J. M., Locke, F. L.. "Outcomes of patients aged 65 years in ZUMA-1, a pivotal phase 1/2 study of axicabtagene ciloleucel (Axi-Cel) in refractory large B cell lymphoma". American Journal of Hematology (2019). 94 (Supplement 2): S19-S20.	Incomplete / insufficient / partial data	This publication only provided subgroup analyses of patients aged 65 years from ZUMA-1.
	Topp MS, Meerten TV, Houot R, Minnema M, Milpied N, Lugtenburg PJ, et al. Earlier Steroid Use with Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL) [abstract] Biology of Blood and Marrow Transplantation. 2020 Mar; 26 Suppl 3:Abstract 135.	Population	Outcomes were only available for a non-randomised safety expansion cohort (cohort 4) that evaluated early steroid use.
	Topp MS, Van Meerten T, Wermke M, Lugtenburg EJ, Minnema MC, Song KW, et al. Earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B cell lymphoma [abstract]. Blood. 2019 134; Suppl 1: Abstract 243.	Incomplete / insufficient / partial data	This abstract did not report all outcomes or baseline characteristics of interest. A more recent publication with longer-term follow-up was available (OS) and a more detailed publication was available for other outcomes.
	Kuhnl A, Roddie C, E T, Menne T, Linton K, Lugthart S, et al. Outcome of High-grade Lymphoma Patients Treated with CD19 CAR-T - Updated Real-world Experience in the UK [abstract]. 2020 Jun 12, 295063:Abstract S243.	Population	This abstract reports real world evidence (RWE) on patients that were treated with axi-cel or tisagen. Relevant outcomes in the study population of interest were not reported.

June 2021 SLR update	Strati P, Varma A, Adkins S, Nastoupil LJ, Westin J, Hagemeister FB, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. Haematologica. 2020.	Population	This is a post-hoc analysis of patients from ZUMA-1 (cohort 1 and 2) and ZUMA-9 at a single site (MD Cancer Centre in the US).
	Jacobson C, Locke FL, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-Term Survival and Gradual Recovery of B Cells in Patients with Refractory Large B Cell Lymphoma Treated with Axicabtagene Ciloleucel (Axi-Cel) [abstract]. Presented at: The 62nd ASH Annual Meeting of the American Society of Hematology (ASH) and Exposition. 2020 2020 Dec 5-8; Virtual Meeting: Abstract 1187.	Incomplete / insufficient / partial data	This is a subgroup analysis of long-term follow-up in “ongoing” responders.
	Jacobson CA, Locke FL, Miklos DB, Vose JM, Lin Y, Budde LE, et al. Outcomes of Patients (Pts) in ZUMA-9, a Multicenter, Open-Label Study of Axicabtagene Ciloleucel (Axi-Cel) in Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL) for Expanded Access and Commercial Out-of-Specification (OOS) Product [abstract]. Presented at: The 62nd ASH Annual Meeting of the American Society of Hematology (ASH) and Exposition. 2020 2020 Dec 5-8; Virtual Meeting: Abstract 2100.	Population	This is the ZUMA-9 trial, an expanded access trial for patients not eligible for ZUMA-1.
	Baird JH, Epstein DJ, Tamaresis JS, Ehlinger Z, Spiegel JY, Craig J, et al. Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. Blood Advances. 2021 5(1):143-55.	Study design	This is an observational study of participants at single centre study (Stanford University, United States), with limited reporting of eligibility criteria.
	Grana A, Gut N, Williams K, Maakaron J, Porter K, William BM, et al. Safety of Axicabtagene Ciloleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma and Leukemia. 2020.	Study design	This is a real-world observational study evaluating safety outcomes.
	Logue JM, Zucchetti E, Bachmeier CA, Krivenko GS, Larson V, Ninh D, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel	Study design	This is an observational study of participants at single centre study (Moffitt Cancer Center, United States).

	in relapsed or refractory large B-cell lymphoma. Haematologica. 2020.		
	Mian A, Wei W, Winter AM, Khouri J, Jagadeesh D, Anwer F, et al. Outcomes and factors impacting use of axicabtagene ciloleucel in patients with relapsed or refractory large B-cell lymphoma: results from an intention-to-treat analysis. Leuk Lymphoma. 2020:1-9.	Study design	This is a real-world observational study evaluating outcomes of an intent-to-treat (ITT) population.
	Pinnix CC, Gunther JR, Dabaja BS, Strati P, Fang P, Hawkins MC, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. Blood Advances. 2020 4(13):2871-83.	Study design	This is a real-world observational study on patients who received bridging therapy.
	Strati P, Nastoupil LJ, Westin J, Fayad LE, Ahmed S, Fowler NH, et al. Clinical and radiologic correlates of neurotoxicity after axicabtagene ciloleucel in large B-cell lymphoma. Blood Advances. 2020 4(16):3943-51.	Study design	This is an observational study of participants at single centre study (MD Anderson Cancer Center, United States).
	Dreger P, Dietrich S, Schubert ML, Selberg L, Bondong A, Wegner M, et al. CAR T cells or allogeneic transplantation as standard of care for advanced large B-cell lymphoma: An intent-to-treat comparison. Blood Advances. 2020 4(24):6157-68.	Study design	This is an observational study for commercial CAR T therapies that includes other treatments.
	Nagle SJ, Murphree C, Raess PW, Schachter L, Chen A, Hayes-Lattin B, et al. Prolonged hematologic toxicity following treatment with chimeric antigen receptor T cells in patients with hematologic malignancies. Am J Hematol. 2021 96(4):455-61.	Study design	This is an observational study for commercial CAR T therapies that includes other treatments and patients that had prolonged hematologic toxicity.
	Sermer D, Batlevi C, Lia Palomba M, Shah G, Lin RJ, Perales MA, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. Blood Advances. 2020 4(19):4669-78.	Study design	Abstract reports RWE for commercial CAR T therapies and includes other treatments not relevant for inclusion.
	Vercellino L, Di Blasi R, Kanoun S, Tessoulin B, Rossi C, D'Aveni-Piney M, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood Advances. 2020 4(22):5607-15.	Study design	Abstract reports RWE for commercial CAR T therapies and includes other treatments not relevant for inclusion.

	Imber BS, Perales M-A, Flynn J, Ruiz JD, Devlin S, Alarcon Tomas A, et al. Clinical Impact of Bridging Therapy Prior to Commercial Chimeric Antigen Receptor (CAR) T-Cell Therapies for Relapsed/Refractory Lymphomas [abstract]. Presented at: The 62nd ASH Annual Meeting of the American Society of Hematology (ASH) and Exposition. 2020 2020 Dec 5-8; Virtual Meeting: Abstract 1448.	Study design	Abstract reports RWE for commercial CAR T therapies and includes other treatments not relevant for inclusion.

Abbreviations: CAR: chimeric antigen receptor; CNS: central nervous system; DCO: data cut-off; ITT: intent-to-treat; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; NHL: non-Hodkin lymphoma; OS: overall survival; PFS: progression-free survival; RWE: real-world evidence; SLR: systematic literature review; US: United States.

MAIC interpretation – clinical similarity

A4. As discussed at the Decision Problem Meeting, a statistically non-significant result from an indirect treatment comparison based on superiority analysis (i.e. without any specified noninferiority or equivalence margins) should not be interpreted statistically as evidence of similarity or equivalence of the therapies being compared. Please would you provide a clear justification for the company's inference that liso-cel and axi-cel have similar clinical effectiveness given that the MAIC results for the clinical effectiveness outcomes do not statistically demonstrate noninferiority or equivalence.

BMS' interpretation of clinical similarity does not solely rely on the MAIC results but, instead, considers the totality of evidence discussed in this response. BMS agree that the MAIC is a descriptive, decision-supporting tool that cannot prove statistical evidence of similarity, non-inferiority, or equivalence. However, the adjusted effect estimates still provide meaningful comparative information. The direction and magnitude of the point estimates (OS hazard ratio [HR]: [redacted] PFS HR: [redacted]), even if non-significant, are clinically relevant. These results demonstrate a positive trend in favour of liso-cel, thus meaning the assumption of clinical similarity between the two treatments can be considered conservative. Additionally, the confidence intervals do not indicate a clinically meaningful disadvantage for liso-cel versus axi-cel. Therefore, the MAIC results provide an indication of clinical plausibility of similar clinical effectiveness.

The primary evidence supporting comparable clinical effectiveness comes from UK CAR T Experts consulted as part of the CS, who unanimously agreed that clinical evidence, so far, has been consistent in demonstrating that liso-cel and axi-cel have comparable efficacy at third-line or later (3L+).[9] Further support exists from multiple US real-world evidence studies, where liso-cel is widely used in routine practice and where no statistically significant differences in median PFS or OS have been observed between the two treatments.[10-12] In one study of 624 patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) receiving CAR T-cell therapy (axi-cel n=344; liso-cel n=138; tisa-cel n=142), median PFS was 18 months for both axi-cel and liso-cel after a median follow-up of 20.9 months with highly comparable 2-year PFS estimates (axi-cel: 46% [95% CI: 40, 53];, liso-cel: 45% [95% CI: 35, 57]). The US RWE studies are deemed to be generalisable to UK clinical practice.

Collectively, evidence from the MAIC, RWE and UK CAR T Expert opinion supports a reasonable inference of clinically similar effectiveness for decision-making, consistent with how NICE routinely assesses and accepts evidence of clinical similarity.

MAIC interpretation – proportional hazards assumption

A5. For PFS (CS page 84, company MAIC Report page 52) and for OS (CS page 86, company MAIC Report page 58) the text states that "Visual inspection of the KM curve and the Grambsch-Therneau test was generally supportive of the proportional hazards assumption for these analyses". However, the text in section 6.2 of the company MAIC Report (page 74) states that "The Grambsch-

Therneau test suggested possible violations of the proportional hazard assumptions for some comparisons of OS and PFS". Please clarify for which analyses the proportional hazards assumption was considered to have possibly been violated. Please provide log cumulative hazard plots for each of the Kaplan-Meier survival analyses to help interpretation of the proportionality of hazards.

The proportional hazards (PH) assumption was evaluated through visual inspection of the Kaplan-Meier (KM) curves and the p-values from Grambsch-Therneau test before and after the MAIC, as discussed in Section B.3.9.5 of the CS. Visual inspection of the PFS and OS KM curves was generally supportive of the PH assumption and was consistent with the results of formal Grambsch-Therneau tests (with all p-values >0.10 indicating limited evidence of violation of the PH assumption).

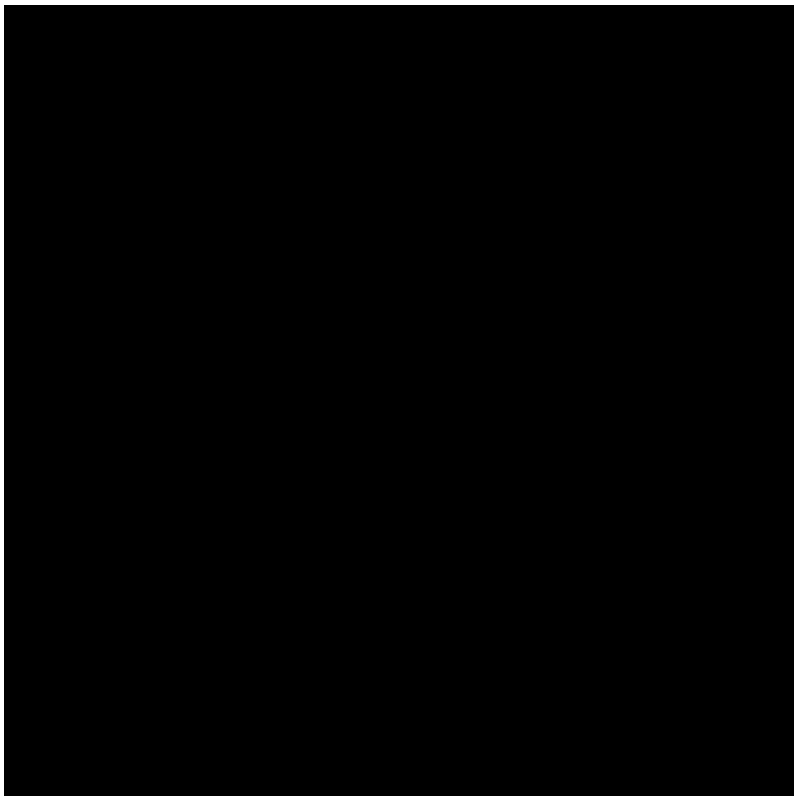
Table 3: p-values from Grambsch-Therneau test for comparison of liso-cel to axi-cel

	p-values from Grambsch-Therneau
PFS	
Naïve	[redacted]
Primary Analysis	[redacted]
Sensitivity Analysis 1	[redacted]
Sensitivity Analysis 2	[redacted]
OS	
Naïve	[redacted]
Primary Analysis	[redacted]
Sensitivity Analysis 1	[redacted]
Sensitivity Analysis 2	[redacted]

Abbreviations: Axi-cel: axicabtagene ciloleucel; Liso-cel: lisocabtagene maraleucel; OS: overall survival; PFS: progression-free survival.

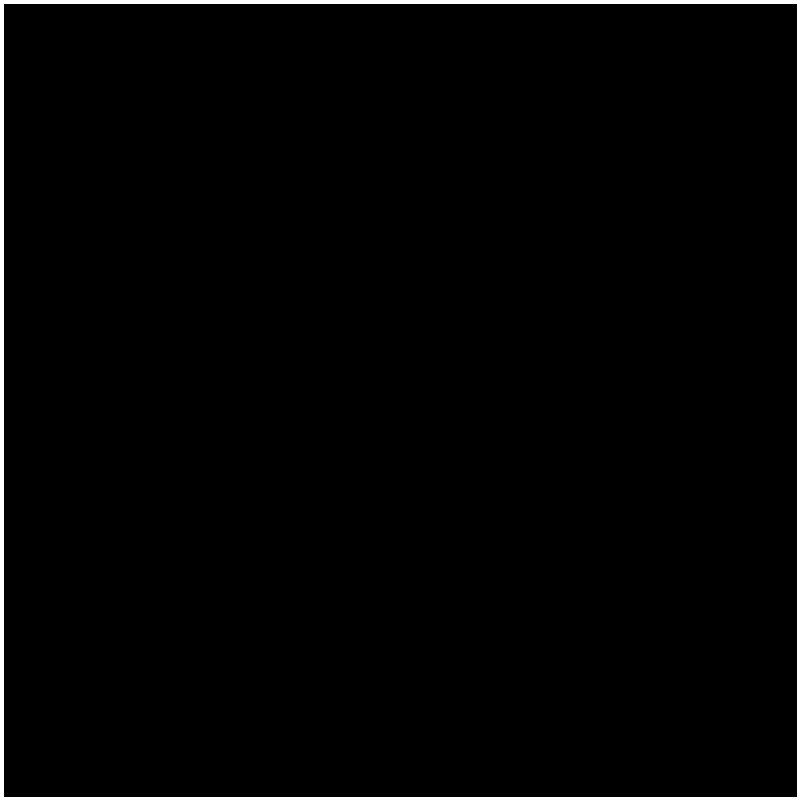
For completeness, the log cumulative hazard plots for PFS and OS for the primary analysis for both treatments are presented in Figure 1 and Figure 2, respectively. Following an initial period of variability, both plots demonstrate proportionality between liso-cel and axi-cel, supporting the conclusion that the PH assumption holds, in line with the associated p-values from the Grambsch-Therneau test (PFS: [redacted]; OS: [redacted]).

Figure 1: Log cumulative hazard plot for PFS (MAIC; Primary Analysis)



Abbreviations: MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.

Figure 2: Log cumulative hazard plot for OS (MAIC; Primary Analysis)



Abbreviations: MAIC: matching-adjusted indirect comparison; OS: overall survival.

A6. Please provide the statistical code that was used for the MAIC analyses

[redacted]

[redacted]

Section B: Clarification on cost-effectiveness data

B1. The CS states that the proportion of patients requiring IVIg for liso-cel and axi-cel were taken from the company's MAIC (CS Table 45). The EAG is unable to find these data in the CS or the MAIC Report. Please would you explain where we can find this information, e.g. the source page or table number.

In the base case, the proportion of patients requiring intravenous immunoglobulin (IVIg) treatment in both arms was informed by the results of the MAIC for adverse events (AEs) of liso-cel versus axi-cel, for hypogammaglobulinaemia. This is reported in the MAIC report: Table 18, page 67; row: "Hypogammaglobulinemia[a], Grouped Term", and in the CS: Table 45, second column. Both MAIC and CS tables report that [redacted]% of liso-cel patients and [redacted]% of axi-cel patients require IVIg, as per the results of the MAIC.[7]

B2. The CS states that the length of ICU stay (CS Table 46) was taken from the TA872 committee papers. The EAG is unable to find these data in the TA872 committee papers. Please provide further information on where we can verify these data.

BMS apologises for the typographical error here. The length of intensive care unit (ICU) stay for patients receiving axi-cel was in fact taken from expert opinion during technical engagement for NICE TA559 (initial recommendation of axi-cel for patients with diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies) and, as such, can be found in the technology appraisal (TA)559 Committee papers (page 618; which are available through the TA872 page).[13] The length of stay was not updated as part of TA872 (Cancer Drugs Fund review of TA559).

B3. The CS reports the pre-treatment proportions of patients for axi-cel taken from Locke et al. 2019 on CS page 102 and in the model (Treatment Inputs!Row35). The EAG are unable to validate these proportions from the source. Please provide the page number of the source where the EAG can find these values.

Patient numbers for treatments prior to axi-cel in the ZUMA-1 trial are provided in Figure S1 of the Supplementary Appendix of the Locke *et al.* 2019 publication (page 17).[6] These values were used to calculate the relative proportions of patients receiving each stage of axi-cel treatment, as presented in Figure 13, page 102. The Supplementary Appendix for Locke *et al.* 2019 is provided as part of the reference pack accompanying this response. BMS apologises for not providing the Supplementary Appendix previously.

B4. The EAG notes that the company have not taken into consideration drug wastage when calculating drug costs for bridging therapies (Treatment Inputs!F78:F91, J78:J91). Please explain how drug wastage is implemented in

the model, or state any assumptions and justifications being made in relation to drug wastage.

Drug wastage for bridging therapies was not included in the cost-comparison model as a simplifying assumption. In the model base case, the proportion of patients receiving bridging therapy, based on clinical opinion, was set to be equal across treatment arms. As such, the inclusion of drug wastage in bridging therapy calculations would have no impact on the relative difference in costs between axi-cel and liso-cel.

B5: The base case and scenario analysis approaches for estimating the proportion of patients requiring ICU admission (CS Table 47) both have limitations. Given that the proportion requiring ICU admission is reported in both the TRANSFORM and ZUMA-1 studies please would the company provide an estimate of the proportion requiring ICU use that adjusts for the differences in population characteristics between the TRANSFORM and ZUMA-1 studies, i.e. using a MAIC approach?

Performing a MAIC to provide an estimate of the proportion of patients requiring ICU admission, adjusting for the differences in population characteristics in TRANSCEND and ZUMA-1, is not feasible within the timeframe of this response. However, BMS considers the data sources used in the base case and scenario analyses for ICU proportions (trial data and French RWE) to be appropriate for informing ICU data for the patient population of interest in this submission, with the scenario analysis providing adequate exploration of the uncertainty around the base case values.

All available evidence consistently show that liso-cel is associated with fewer ICU admissions compared with axi-cel, reflecting its more favourable safety profile. Given ICU admissions are typically associated with the management of Grade ≥3 CAR T specific AEs (namely cytokine release syndrome [CRS] and neurotoxicity [NT]), and comparative evidence from the MAIC show [redacted] of these AEs with liso-cel compared with axi-cel (Grade ≥3 CRS odds ratio [OR]: [redacted]; NT OR: [redacted]), the difference in ICU admissions is clinically well-supported.[7] This was specifically highlighted by clinicians in NICE TA1048 who noted that the key difference between liso-cel and axi-cel is the safety profile, and that substantially fewer Grade 3 and 4 AEs are expected for people receiving treatment with liso-cel compared with axi-cel, as reported in Section B.4.1 of the CS.[14, 15]

French RWE was used in the base case as it provides more recent data than the TRANSCEND and ZUMA-1 trials and, therefore, is expected to be more reflective of current clinical practice (i.e. the use of bridging therapies to debulk the disease) and any advancements in the management of CAR T specific AEs (specifically ICANS and CRS) that typically result in ICU admission.[16] This was supported by clinicians in NICE TA1048 that stated that clinicians now have increased experience in managing AEs associated with CAR T therapy.[14] Of note, the 2022–2023 results from this study were accepted as part of NICE TA1048 to inform ICU admission rates following CAR T-cell therapy at second-line (2L).[14, 17] Finally, management of Grade ≥3 CRS and ICANS is comparable between France and England because both health systems follow internationally standardised American Society for Transplantation and Cellular Therapy (ASTCT)-based algorithms involving tocilizumab, corticosteroids, and ICU escalation for severe toxicity.[18, 19]

The base case uses RWE from 2L liso-cel use to inform ICU admissions associated with third-line (3L) liso-cel use in the model (as reported in Section B.4.2.3 of the CS). Feedback from UK CAR T Experts validated that ICU rates for 2L CAR T therapy are expected to be comparable to those at 3L

for the same therapy, supporting the extrapolation of ICU rates associated with 2L liso-cel to 3L in the base case.[9]

In order to assess any uncertainty associated with these data, a scenario analysis was conducted using data from the TRANSCEND trial (study initiation: 2016), and US RWE based upon ZUMA-1 Cohort 4 (2021).[20, 21] These data demonstrate a [redacted] in the proportion of patients requiring ICU admission following treatment with liso-cel and axi-cel ([redacted]% versus 16.33%, respectively).[21, 22] This is [redacted] than the [redacted] difference reported in French RWE (liso-cel [redacted]%; axi-cel: [redacted]%).[16] As above, the [redacted] difference observed between the two trial-based sources compared with the French RWE is likely reflective of advances in the management of AEs that typically result in ICU admission, since the initiation of the TRANSCEND clinical trial.

Although the base case shows an [redacted] difference and the scenario analysis a [redacted] difference in ICU admission rates between liso-cel and axi-cel, the associated incremental cost impact is minimal (–£[redacted] vs –£[redacted]; a difference of ~£2,500). Given this negligible effect on total costs, ICU data does not materially influence model outcomes and should not be considered a key uncertainty within the submission.

In addition, BMS notes a typographical error in question B5 – please could “TRANSFORM” be updated to “TRANSCEND”.

B6: Section H1 of the appendix does not include the exact strength and pack size for the treatments used in the model. Please provide the exact 'pack/vial size', 'units per pack/vial' and ‘cost per pack/vial’ used for each comparator and subsequent treatment in your economic model.

Given subsequent treatment choices depend on prior treatment lines, UK CAR T Experts confirmed that patients treated with liso-cel or axi-cel at 3L+ are expected to receive similar 4L+ treatments.[9] As such, subsequent treatments (and therefore their associated costs) were assumed to be equal between the two treatment arms across all model years. These costs were therefore not included in the cost-comparison analysis.

Axi-cel is the sole comparator considered in the cost-comparison analysis. Axi-cel is administered as a single intravenous (IV) infusion of CAR-transduced autologous T-cells at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg, with a list price per infusion of £280,451.00.

All bridging therapies included in the model including pack/vial size, units per pack/vial and cost per pack/vial are detailed in Table 4.

Table 4: Bridging therapies included in the cost-comparison model

Drug name	Unit Size (mg)	Units per Pack	Cost per Pack
Rituximab	500	1	£785.84[23]
Gemcitabine	1000	1	£13.53[24]
Oxaliplatin	100	1	£35.85[24]
Bendamustine	100	5	£64.29[24]
Polatuzumab vedotin	30	1	£2,370.00[25]
Cisplatin	100	1	£30.50[24]
Ifosfamide	2000	1	£298.41[26]
Carboplatin	600	1	£21.85[24]
Etoposide	500	1	£35.78[24]
Dexamethasone	4	30	£8.94[24]

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool.
Sources: eMIT (2025);[24] BNF, Rituximab;[23] BNF, Ifosfamide;[26] BNF, polatuzumab vedotin.[25]

Section C: Textual clarification and additional points

The EAG has no textual clarifications at this stage

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and follicular lymphoma grade 3B, after two or more lines of systemic therapy [ID6619]

NICE medicines optimisation briefing

Nov 2025

Key issues

- No responses were received from the survey therefore we have no system intelligence to advise on current practice.
- It is not clear what the main comparator(s) are for the three different indications.
- There is a licensed chimeric antigen receptor T-cell (CAR-T) therapy at the same place in therapy for diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma.
- There is no licensed CAR-T therapy comparator for follicular lymphoma grade 3B.

Technology overview

Lisocabtagene maraleucel (Breyanzi) is a CD19-directed genetically modified autologous cell-based product, chimeric antigen receptor T-cell (CAR-T) therapy. CAR-T therapy uses T-cells from the patient, which are genetically modified to specifically target and destroy cancer cells. This is a personalised cancer treatment which can only be administered to the patient whose T-cells have been genetically modified.

Lisocabtagene maraleucel is administered as a single dose for infusion. Patients must have lymphodepleting chemotherapy 2 to 7 days before the infusion. Tocilizumab should also be available for use during

treatment in the event of cytokine release syndrome (summary of product characteristics [SPC] for lisocabtagene maraleucel)

Lisocabtagene maraleucel is licensed in the UK for treating:

- 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) in adults who have relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.
- Relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.
- Relapsed or refractory follicular lymphoma after two or more lines of systemic therapy (SPC).

NICE has recommended lisocabtagene maraleucel as an option for treating DLBCL, HGBCL, PMBCL and FL3B that is refractory to, or has relapsed within 12 months after first-line chemoimmunotherapy (TA1048).

Context

Lymphomas are cancers of the lymphatic system. They are divided into Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphomas (NHL) are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. High-grade NHL is an aggressive, fast-growing form of the disease.

The most common high-grade NHL is DLBCL. There are other forms of high-grade NHL. These include PMBCL and FL3B. FL3B is usually treated the same as DLBCL.

The NICE Non-Hodgkin's lymphoma: diagnosis and management guideline (NG52) includes management recommendations for DLBCL.

No responses were received from the survey therefore we have no system intelligence to advise on current practice.

Relapsed or refractory diffuse large B-cell lymphoma

At this point of the treatment pathway for relapsed or refractory DLBCL, after two or more lines of systemic therapy, NICE have recommended several treatments.

Four immunotherapies are recommended after 2 or more lines of systemic therapy, polatuzumab vedotin with rituximab and bendamustine (TA649), glofitamab (TA927), epcoritamab (TA954) and loncastuximab tesirine (TA947).

One CAR-T therapy is recommended after 2 or more lines of systemic therapy, axicabtagene ciloleucel (TA872).

Salvage chemotherapy combination regimes with or without rituximab are also an option at this point of the treatment pathway.

Relapsed or refractory primary mediastinal large B-cell lymphoma

At this point of the treatment pathway for relapsed or refractory PMBCL, after two or more lines of systemic therapy NICE have recommended 1 CAR-T therapy, axicabtagene ciloleucel (TA872).

Salvage chemotherapy combination regimes with or without rituximab are also an option at this point of the treatment pathway.

However, polatuzumab vedotin with rituximab and bendamustine, glofitamab, epcoritamab and loncastuximab tesirine are recommended as an option by NHS England for relapsed or refractory PMBCL, after two or more lines of systemic therapy (NHS England Cancer Drugs Fund list).

Follicular lymphoma grade 3B

Salvage chemotherapy combination regimes with or without rituximab are an option at this point of the treatment pathway.

Axicabtagene ciloleucel is recommended as an option by NHS England for FL3B, after two or more lines of systemic therapy (NHS England Cancer Drugs Fund list). This is an off-label use.

Current practice

CAR-T therapy is part of the Advanced Therapy Medicinal Products (ATMP) Programme in the NHS England highly specialised services portfolio. The programme commissions and prepares the NHS for ATMPs as these products require a greater level of commissioning support, and a national approach is required.

Currently 20 hospitals in England have specialist centres that are commissioned to deliver CAR-T therapy to young people up to the age of 25 years old and adults. A national panel of expert clinicians decides whether someone is eligible for treatment following a referral from a specialist doctor. No responses were received from the survey therefore we have no system intelligence to further advise on current practice.

Patient centred factors

CAR-T therapy is a highly complex treatment which is only commissioned in certain centres. Lisocabtagene maraleucel is a single infusion, however prior to administration, patients must have lymphodepleting chemotherapy 2 to 7 days before the infusion. Tocilizumab should also be available for use during treatment in the event of cytokine release syndrome, a potentially fatal or life-threatening reaction which can occur following lisocabtagene maraleucel treatment.

After the infusion of lisocabtagene maraleucel, patients should be monitored 2-3 times during the first week for signs and symptoms of potential CRS, neurologic events and other adverse events. Monitoring

should be continued for a least 4 weeks after infusion and patients are advised to remain close to the treatment centre during those 4 weeks.

Health inequalities

There are many different types of NHL and there are no UK wide survival statistics available for all the different types and stages of high-grade NHL. Survival statistics are available for DLBCL, around 60 in 100 people will survive 5 years or more after their diagnosis. Around 5500 people are diagnosed with DLBCL each year in the UK. It can develop at any age, but it is rare in children and is more common in older people. Most people diagnosed with DLBCL are 65 or over. DLBCL affects slightly more men than women.

There are 20 specialist centres across England commissioned to deliver CAR-T therapy. This could lead to health inequalities in accessibility for people living in more remote areas of the UK, people who would need to travel long distances or people who may have difficulties travelling due to co-morbidities or disabilities.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments (review of TA987) [ID6619]

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.

About you

1.Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Anthony Nolan is a charity that connects patients in need of a stem cell transplant with suitable stem cell donors. The charity undertakes research to improve treatments for blood cancers and disorders, with a focus on enhancing the effectiveness of stem cell transplants. Anthony Nolan is funded through a combination of donations from individuals and organisations, alongside service fees paid by transplant centres in the UK and internationally. Anthony Nolan has approximately 400 employees.
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, Anthony Nolan has received funding from Gilead Sciences Ltd in 2025: • Grant of £30,000 towards Anthony Nolan's Patient Grants Service. • Grant of £15,000 to support Anthony Nolan's work with One Voice Blackburn – Growing and Diversifying the Anthony Nolan Stem Cell Register. • £900 speaker fees for attendance at two roundtables organised by Gilead.
4c. Do you have any direct or indirect links	None.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to patients and families who have received CAR-T and have experience of lymphoma. We also spoke with clinicians who manage CAR-T patients including DLBCL patients.

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?	• Living with relapsed or refractory DLBCL is all consuming. Patients have had several prior intensive treatments, and are likely to have experienced lots of side effects from the cumulative treatment burden. • Patients will have relapsed or not responded to at least two other treatments, this can be very difficult emotionally and psychologically. In some cases will have been in remission for several years or months prior to relapse, which is devastating. • Patients often experience significant emotional, social and physical impacts. Common effects include fatigue, night sweats, sickness, nausea, anxiety, depression and social isolation. The specific challenges vary depending on the part of the body affected; for example, lymphoma in the chest or lungs can cause breathlessness. • Carers often assume significant emotional and practical responsibilities in supporting patients, ranging from assistance with daily activities to actively coordinating care, such as arranging medical appointments and monitoring for health concerns (e.g. signs of infection). This sustained responsibility can lead to carer burnout, including emotional, physical and mental exhaustion.

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 and carers think it is incredibly important to have the option of a potentially curative therapy like CAR-T available in the third line setting when prior treatment lines have not been successful. They also think that current treatments could have fewer side effects and would appreciate having the option to spend less time in hospital and having to travel long distances to access care.
8. Is there an unmet need for patients with this condition?	• At present, there is only one existing CAR-T option for patients in this setting. There is an unmet need for another potentially curative option that has a lower toxicity burden and would therefore be suitable for patients who cannot currently access CAR-T, for example those who are more frail.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	• Patients and carers really value having a choice of CAR-T therapies, and having CAR-T options that are less likely to cause significant side effects. • Patients and carers are also very supportive of treatments like liso-cel that are safe enough to deliver in ambulatory facilities, allowing them to spend less time in hospital.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	• As with any CAR-T or cell therapy option, there are potentially significant side effects of this treatment and there is still a requirement for patients and carers to spend large amounts of time and money travelling to and from hospital and as inpatients.

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.	• Liso-cel is a particularly important option for patients who cannot access the only CAR-T option currently available, because the evidence indicates that liso-cel has fewer side effects. This means that liso-cel would be of particular benefit to patients who are older and those with co-morbidities.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• Patients with relapsed or refractory large B-cell lymphoma after one prior systemic therapy can access two CAR-T options. We believe it is important that patients with the same disease but who have not been offered a CAR-T earlier in the pathway and have relapsed or have refractory disease at third line can also have the same level of choice as patients at second line.

Other issues

13. Are there any other issues that you would like the committee to consider?	• Liso-cel offers patients a relatively good safety profile, this reduces the burden on NHS bed capacity, and improves patient and carer experience.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients and carers with relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments experience significant negative impacts on the physical and mental health and overall quality of life due to this severe disease. • CAR-T therapy is the only potentially curative treatment available to patients in this setting. • Liso-cel has fewer side effects than the existing CAR-T option and could be offered to patients who would not otherwise have a curative treatment option, such as those who are older. • Liso-cel can be administered in am ambulatory model which is highly valued by patients and carers and reduces the burden on NHS capacity. • Patients and carers feel that having a choice of treatment options is very important.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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- Your response should not be longer than 10 pages.

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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 most common blood 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 leading 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 Squibbs, £10,000
	  ○ Contributed towards our mission and objectives
	• AbbVie, £15,000
	  ○ Contributed towards our Information Provision, Helpline and Live Your Life workshops
	• Gilead Sciences Ltd, £14,000
	  ○ Contributed towards our Preparing for Treatment service and Lymphoma Essentials
	  ○ Sponsorship of our Lymphoma Information Days
	• Pfizer, £4,000
	  ○ Sponsorship of our Lymphoma Information Days
	• Roche, £25,000
	  ○ Contributed towards our Information Provision and Peer Support Services
	  ○ Sponsorship of our Lymphoma Management course for HCPs

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
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 most common blood 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 are commonly 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 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 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 eligible, 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, or bispecific antibody therapies. 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 in the third line setting would be hugely beneficial, particularly potentially curative therapies like CAR-T. *"As many treatment options are needed as possible to improve statistical chances of a cure".* • There is currently only one existing CAR-T option for patients in this setting. Liso-cel, with its lower toxicity burden, would be a valuable addition, particularly for patients who are currently not suitable for CAR-T due to, for example, age-related frailty. • Patients prefer treatments with fewer side effects. The 2024 Lymphoma Coalition survey (1204 UK responses) indicated that 72% of patients and 80% of carers rated fewer side effects/more tolerable side effects during treatment as being important or very important. • Patients also prefer having the option to spend less time in hospital or having to travel long distances to access treatment.

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 other treatments had failed would be a huge advantage of this treatment. *"Very good to have more treatment options".* • The potential to administer the treatment in an outpatient setting or spend less time in hospital while receiving the treatment is a significant benefit. Patients appreciate a treatment which requires less time in hospital, and therefore less disruption to them and their carers. • The reduced need for intensive, long-term rehabilitation following neurotoxicity is a substantial advantage for patients in terms of their quality of life, both in terms of shorter duration of rehabilitation and a reduced likelihood of the trauma burden of an ITU stay. • 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 disadvantage identified by our patients is the risk of cytokine release syndrome.

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 available. • 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 impact carers and loved ones. • The lower toxicity burden of liso-cel offers significant advantages in terms of both eligibility and quality of life.

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Cost Comparison Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments (review of TA987) [ID6619]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	Clatterbridge Cancer Centre and The Royal College of Pathologists
3. Job title or position	Consultant
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	It is Regional referral centre for Haem-Onc patients and a University Hospital. NHS funded.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure high grade lymphoma in 3rd line setting
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Cure – improved Overall survival in comparison to SOC (chemotherapy and autograft consolidation) comparable OS with Axi-cel treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – Axi-cel provides good OS benefit but is a toxic approach given the CRS/ICANs rate in a population with a medium age around 65yrs old. A less toxic but efficacious curative approach is needed

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	3rd line plus patients are treated with Axi-cel if deemed fit via NCCP panel
9a. Are any clinical guidelines used in the	BSH guidelines

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The treatment algorithm is clear – but there is some regional variation – some centre have a culture of using more bispecific antibodies.
9c. What impact would the technology have on the current pathway of care?	Give an option to treat less fit patients with CAR T more safely in 3rd line plus.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	No
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Designated CAR T centres only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There is established use of Liso-cel in 2nd line treatment and axi-cel is already used in 3rd line. Given the lower toxicity of Liso-cel there might be an increase in CAR T use in 3rd line which could require some investment – ambulatory care/inpatient beds/PET scanning etc.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Compared to Axi-cel -the lower associated ICANs/CRS will ITU admission rate, associated treatment morbidities and likely reduce TRM.
11a. Do you expect the technology to increase length of life more than current care?	It would do in the frailer population who would not be treated with Axi-cel, but were deemed axi-cel-fit – who otherwise would be treated with a bispecific antibody
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially as less toxic than Axi-cel
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with significant co-morbidities would tolerate the treatment worse than the general population.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	In comparison to Axi-cel: The longer manufacturing time may lead to more bridging required/more chance for disease progression pre infusion. There will be certain cases where the cadence of the lymphoma progression will be so rapid that Axi-cel could be preferential in these cases.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is likely however that Liso-cel will be better tolerated – less severe CRS/ICANs – therefore less protracted inpatients stays (more feasible for more outpatient/ambulatory monitoring).
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In comparison to Axi-cel - given its lower side effect profile, and risk of ITU admission and protracted inpatient stays – the patients are likely to have improved quality of life. The progression free survival in comparison with Axi-cel is similar (possibly very slightly lower with liso-cel -but no RCT between 2 products). This means that the QALYs will likely be at least high as with aci-cel
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes it would make a significant impact in the less fit/older patients requiring 3rd line therapy for RR DLBC Lymphoma -giving them a more tolerable treatment option
16a. Is the technology a 'step-change' in the management of the condition?	This is not a step change

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – less fit patients needing 3rd line Rx for DLBC L
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects which could lead to a prolonged inpatient stay include ICANS, CRS and infections. Patients would be at significantly increase risk of atypical and overwhelming infection for the year following treatment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The TRANSCEND study showed that at 3rd line treatment for RR DLBC L showed that liso-cel had a manageable side effect profile - better than axi-cel (in terms of Grade 3+ CRS/ICANs) and similar OS data (50% vs 58% in Zuma 1) . It showed also significantly better than expected outcomes with previous SOC autograft post salvage – though this was not directly compared as an RCT. There is data to suggest that autografting fit patients who achieve a PR to 2nd line treatment should still be the standard of care.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	OS, Grade 3+ toxicity, duration of inpatient stay and TRM. All measured in trial

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not yet.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA872?	No
21. How do data on real-world experience compare with the trial data?	Lysa Real world data but in second line treatment shows similar mOS and toxicity. Japanese study group showed comparable outcomes in 3rd line settting (107 patients)
22. Does axicabtagene ciloleucel (NICE recommendation TA872) provide similar health benefits to lisocabtagene	The OS rate with Axicel shows a slightly better OS in Zuma 1. However given the medium age of presentation of DLBC is 64-67yrs the lower toxicity profile with liso cel will lead to less morbidity, shorter

maraleucel after 2 or more systemic treatments?	inpatient stays, fewer ITU admissions and the scope for more ambulatory care – improving patient QOL and associated treatment costs.

Equality

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are data showing that people in more deprived areas of the country (like the North West) are less likely to receive CAR T treatment. All efforts should be made to improve access to this curative treatment. Given the population in more deprived areas tend to be more co-morbid – a less toxic CAR construct might improve uptake of this approach in these areas
23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• It shows near comparable efficacy to axi-cel in terms of OS in 3rd line • It is more tolerable with lower TRM • There is more scope for delivering liso-cel in an ambulatory setting. • Longer manufacturing time Vs axi-cel make liso-cel potentially less attractive in proliferative disease – especially where bridging options are limited. •

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External Assessment Group (EAG) Report

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments (review of TA987) [ID6619]

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Dr Jeffery Smith, Consultant Haematologist, The Clatterbridge Centre NHS Foundation Trust

Dr Harriet Walter, Associate Professor of Medical Oncology, University of Leicester and University Hospitals Leicester

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Declared competing interests of the authors and advisors

None from the authors or Dr Walter.

Dr Lown received honoraria from Bristol-Myers Squibb (BMS) (manufacturer of lisocabtagene ciloleucel) for the following activities: (i) presented a talk at the London Lymphoma Forum on second-line lisocabtagene maraleucel which discussed the TRANSFORM trial (not included in the company submission) and real-world experiences with lisocabtagene maraleucel in the second-line setting; (ii) contributed to two BMS anonymized advisory boards (one UK, one European, neither relating to the company submission) discussing CAR-T cell therapy in general; and (iii) contributed to a Digital Twin tool (collaboration between BMS and Ernst and Young) to model the economics of ambulatory versus inpatient CAR-T cell delivery. Dr Lown also received honoraria from Gilead (manufacturer of axicabtagene ciloleucel) for travel, accommodation and/or registration support for: (i) local ‘Update on CAR-T’ talks which included discussions of referral pathways and optimising CAR-T delivery

(but not clinical or economic evidence) for both lisocabtagene maraleucel and axicabtagene ciloleucel in currently reimbursed lines (including third-line); and (ii) attendance at the American Society of Haematology Annual Meeting (ASH) in Orlando, December 2025. Dr Lown confirms that none of these activities included discussion of clinical effectiveness, safety, or cost-effectiveness evidence for the intervention (lisocabtagene maraleucel) or comparators (including axicabtagene ciloleucel) in the present indication (third-line therapy) and that he did not make any contribution to the company's submission.

Dr Smith received speaker honoraria from Abbvie (manufacturer of epcoritamab) (2025), Gilead (manufacturer of axicabtagene ciloleucel) (2024) and Roche (manufacturer of glofitamab, polatuzumab vedotin, and rituximab) (2025). He also received conference registration support from Gilead for the American Society of Hematology annual meeting 2024 and from Roche for the European Haematological Association 2024 Annual meeting. Dr Smith confirms that these activities did not involve any work related to the company submission.

Rider on responsibility for the 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 the authors

Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor; Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report; Asyl Hawa critically appraised the economic evaluation, and drafted the report; Keith

Cooper critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the indirect treatment comparison and drafted the report.

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- EAG report Table 10
- Information in part of EAG report Table 3

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List of Abbreviations

3L+	Third line or later
AE	Adverse event
AESI	Adverse event of special interest
ASCT	Autologous stem cell transplant
Axi-cel	Axicabtagene ciloleucel
BNF	British National Formulary
CAR-T	T-cell chimeric antigen receptor
CI	Confidence interval
CR	Complete response
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
DL1	Dose level 1
DL2	Dose level 2
DHAP	Dexamethasone, cytarabine, cisplatin
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
ESHAP	Etoposide, methylprednisolone
ESS	Effective sample size
FAC	Factual accuracy check
FDA	US Food and Drug Administration
FL3B	Follicular lymphoma grade 3B
GDP	Gemcitabine, dexamethasone and cisplatin
HGL	High grade lymphoma
HRG	Healthcare Resource Group

HSCT	Haematopoietic stem cell transplant
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INV	Investigator assessment
IPD	Individual patient level data
IPI	International Prognostic Index
IRC	Independent Review Committee
ITC	Indirect treatment comparison
IV	Intravenous
IVE	Ifosfamide, epirubicin and etoposide
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
Liso-cel	Lisocabtagene maraleucel
MAIC	Matching adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PET	Positron emission tomography
PFS	Progression free survival
PMBCL	Primary mediastinal B-cell lymphoma
Pola-BR	Polatuzumab vedotin, bendamustine and rituximab
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
R-ICE	Rituximab, ifosfamide, carboplatin and etoposide
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SMD	Standardised mean difference

SOC	Standard of care
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States

1 Executive Summary

1.1 Summary of the EAG's view of the company's cost-comparison case

The EAG's comments on the company's cost comparison case are summarised for each of the NICE cost comparison criteria in Table 1.

Table 1 Criteria for cost-comparison technology appraisal

Criteria	Criteria met? Yes/no	EAG considerations
The technology's expected licensed indication is the same as the chosen comparators	Yes	The company's selected comparator, axicabtagene ciloleucel (axi-cel), is used for the same population group and same position in the treatment pathway as the company's licensed indication for the intervention, lisocabtagene maraleucel (liso-cel). That is, people who have relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy and are suitable for T-cell chimeric antigen receptor (CAR-T) therapy.
The chosen comparator meets NICE's criteria for cost-comparison	Yes	Axi-cel has a similar mechanism of action to liso-cel (both are CAR-T therapies) and the EAG's clinical experts agreed that axi-cel has become the current standard of care for those suitable for CAR-T therapy who are refractory after two or more lines of systemic therapy.
It is plausible that the technology may incur similar or lower costs	Yes	The company has submitted a cost comparison model which compares the total costs for liso-cel with axi-cel. The

Criteria	Criteria met? Yes/no	EAG considerations
compared with the comparators.		company's model assumes similar overall survival and progression between liso-cel and axi-cel and that subsequent treatments would also be similar. The EAG's clinical experts agreed that liso-cel and axi-cel are likely to have similar clinical efficacy and liso-cel has a more favourable safety profile than axi-cel. The company's results suggest that liso-cel had an incremental cost of [redacted] with axi-cel when using the discounted patient access scheme (PAS) price for liso-cel and list price for axi-cel. We report results for the company's and EAG's analyses using all available NHS price discounts for axi-cel and the bridging therapies in a confidential addendum to this report.

1.2 The decision problem: summary of the EAG's critique

The company's decision problem population is narrower than the NICE scope, specifically focusing on patients suitable for CAR-T therapy. This is appropriate as it matches the population for which the comparator therapy (axi-cel) was assessed (TA872).[1]

The EAG's full critique of the decision problem is provided in section 3 below.

1.3 The clinical effectiveness evidence: summary of the EAG's critique

The company's primary evidence for clinical efficacy and safety of liso-cel, when used at third line or later for people who have relapsed or refractory large B-cell lymphoma, is from an unanchored matching-adjusted indirect treatment comparison (MAIC). This is appropriate since only single-cohort studies of liso-cel (primarily the TRANSCEND study)[2, 3] and axi-cel (the ZUMA-1 study)[4, 5] are available, precluding a direct head-to-head comparison. However, results of the MAIC are uncertain due to several methodological limitations and ambiguities (section 4.3.7 below).

The EAG's three clinical experts all agreed, independently, that despite the substantial limitations of the MAIC analysis approach, the evidence provided by the company is sufficient to conclude that liso-cel has similar clinical efficacy, and a more favourable safety profile, than axi-cel.

1.4 The cost-effectiveness evidence: summary of the EAG's critique

The company provided a cost comparison model that estimates the difference in costs between liso-cel and axi-cel when used at third line or later for relapsed or refractory large B cell lymphoma. The company's model assumes similar overall survival and progression between liso-cel and axi-cel and that subsequent treatments would also be similar.

The EAG identified and corrected a minor error in the calculation of the bridging therapy R-ICE (rituximab, ifosfamide, carboplatin and etoposide) cost, but this has no effect on the incremental costs of liso-cel compared to axi-cel.

The company's results suggest that liso-cel has an incremental cost of [redacted] compared with axi-cel when using the discounted patient access scheme (PAS) price for liso-cel and the list price for axi-cel. We report results for the company's and EAG's analyses using all available NHS price discounts for axi-cel, and the associated bridging therapies, in a confidential addendum to this report.

2 Background

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Bristol-Myers Squibb on lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after two or more systemic treatments. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 15th December 2025. A response from the company via NICE was received by the EAG on 21st January 2026 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Intervention mechanism of action

The intervention, lisocabtagene maraleucel (liso-cel) and its mechanism of action are well described by the company (CS Table 2). Liso-cel is a T-cell chimeric antigen receptor (CAR-T) therapy, which is a directed genetically modified autologous cellular immunotherapy. Liso-cel targets CD19-expressing cells, including B-cell malignancies, using similar mechanisms to those of cytotoxic T-cells.

CAR-T therapy uses a patient's own T-cells which are taken from the patient in a process called leukapheresis and then modified genetically before being re-introduced in the patient by intravenous (IV) infusion (i.e. autologous use). The genetic modification includes the anti-CD19 domain which is responsible for recognising the lymphoma cells, a transmembrane domain (CD28), an internal signalling domain (CD3) and a co-stimulatory domain (4-1BB) (CS Figure 1).

The general mechanism of action of liso-cel is similar to that of other CAR-T therapies, including the comparator in the company's decision problem for this technology appraisal, axicabtagene ciloleucel (axi-cel). However, unlike other CAR-T therapies, the manufacturing process for liso-cel (CS Figure 2) enables the therapy to include precisely defined proportions of helper T-cells (CD4 T-cells) and cytotoxic

T-cells (CD8 T-cells). The number and ratio of CD4 to CD8 cells is relevant as it influences the strength of the patient's immune response. The company argue that a more favourable safety profile of liso-cel than axi-cel (as described in section 4.2.6 below) might reflect effects of the 4-1BB co-stimulatory domain, lower variability in the total and CD8+ T cells, and the defined 1:1 ratio of CD8+ and CD4+ cells (CS section B.3.9.5, page 87).

The EAG's clinical experts commented that there are three differences between liso-cel and axi-cel which reflect that CAR-T cell manufacture is more complex for liso-cel than for axi-cel:

Manufacturing time for liso-cel (time from leukapheresis to Qualified Person release) is longer than for axi-cel. One of the of the EAG's clinical experts said that at their practice this time is currently 25 to 32 days for liso-cel and 17-21 days for axi-cel. The expert explained that, following Qualified Person release, time to delivery to the patient in their practice has been 8-10 days for liso-cel and 5-6 days for axi-cel. The company clarified in their factual accuracy check (FAC) of this report that the 90th percentile manufacturing time for liso-cel since product launch in March 2025 has been between 32 and 36 days, and that the time to delivery following Qualified Person release can be as low as 5 to 7 days, but can vary if delivery falls over a weekend or sites choose to delay delivery. Patients who are awaiting CAR-T therapy may receive bridging therapy to stabilise their disease (see section 2.2.4 below).

- One EAG clinical expert stated that patients need to have more lymphocytes available for manufacture of liso-cel, which might select fitter patients to receive the therapy. The company clarified in their FAC document that there is no minimum pre-leukapheresis lymphocyte count requirement for liso-cel manufacture, but manufacture can be challenging if the patient has a very low lymphocyte count.
- There is a slightly higher risk of manufacturing failure for liso-cel than for axi-cel, or that the manufactured CAR-T cell product does not strictly meet the intended therapy definition and is regarded as a 'non-conforming product'. In NHS clinical practice patients may receive a non-conforming product only if approved by a national Out of Specification Panel. One of the clinical experts

stated that they would likely offer the patient axi-cel instead of considering a non-conforming product. The experts expect manufacturing failure and frequency of non-conforming products to decline as experience with manufacture and use of liso-cel increases.

2.2.2 Intervention posology

The quantity and proportions of CD8+ and CD4+ T cells in a liso-cel infusion is referred to by the company as the dose level (DL) (CS section B.3.3.1). Dose level 1 (DL1) has 50 x 10^6 CAR-T cells in total, equally divided between CD8+ and CD4+ cells (i.e. 1:1 ratio) whilst dose level 2 (DL2) has 100 x 10^6 CAR-T cells, also with CD8+ and CD4+ cells in equal proportions. The company's pivotal clinical study included patients who received a single or double infusion of DL1, or a single infusion of DL2 (CS Table 7). The EAG's clinical experts commented that only a single infusion of DL2 would be used in NHS clinical practice; however, as explained in section 4.2.2.2 below, the experts agreed that inclusion of DL1 in the clinical study is unlikely to raise major concerns about the generalisability of the dosing to NHS clinical practice.

2.2.3 Intervention pre-treatments

Administration of liso-cel requires the administration of the following pre-treatment therapies:

- Lymphodepleting chemotherapy (LDC) over 3 days, before liso-cel infusion; fludarabine and cyclophosphamide were used as LDC in the clinical studies (CS Table 2). The EAG's clinical experts said that LDC would be similar across CAR-T therapies, except that the cyclophosphamide dose on the liso-cel pathway is 300 mg whereas on the axi-cel pathway it is 500 mg.
- Antihistamine (diphenhydramine hydrochloride or equivalent) plus acetaminophen, 30-60 minutes before liso-cel infusion (CS Table 2).
- Tocilizumab or equivalent for treating cytokine release syndrome (CRS) and other emergency therapies or equipment must be available on site before liso-cel infusion is permitted (CS Table 2).

The Summaries of Product Characteristics for both liso-cel[6] and axi-cel[7] show that, apart from the dose of LDC, the pre-treatments do not differ between products, and the EAG's clinical experts confirmed this reflects clinical practice.

2.2.4 Bridging therapy

Patients awaiting a CAR-T infusion may receive bridging therapy. That is, an anti-cancer therapy to stabilise the patient's disease whilst CAR-T cells are being manufactured (CS section B.3.3.1). The EAG's clinical experts noted that the choice of regimen for bridging therapy varies depending on a patient's previous treatments but would be unlikely to differ systematically between patients who receive liso-cel and those who receive axi-cel. The experts gave different perspectives on how bridging therapy relates to prognosis. One expert said that patients who do not require bridging are usually more stable, with slower disease progression, and may receive targeted radiotherapy to local disease sites. As such, they may have less aggressive disease when they receive CAR-T therapy, with a more favourable overall survival. Another expert explained that as bridging therapy debulks the disease and therefore improves outcomes and reduces toxicity it is a useful management approach for optimising patients in preparation for their CAR T-cell infusion. The expert commented that in their experience most patients would receive bridging therapy, to stabilise their disease, and in that expert's centre liso-cel patients had not required more bridging therapy than axi-cel patients. Overall, the three experts agreed that prognosis with or without bridging therapy is typically influenced by an individual patient's disease characteristics and treatment history and therefore variable but would be unlikely to differ systematically between patients on liso-cel and axi-cel pathways.

2.2.5 Treatment pathway

The EAG's clinical experts agreed with the company's depiction of the treatment pathway in CS Figure 3. The experts noted a typographic error in the Figure (a connecting line should be added to show that patients who relapse or lack response following second-line CAR-T therapy have third-line treatment options), but this has no bearing on the present appraisal of liso-cel at third-line or later.

2.2.6 Subsequent treatments

CS Figure 3 does not include any subsequent treatments that patients would receive after being given liso-cel or axi-cel at third-line or later (3L+), or subsequent treatments for patients who were eligible for but did not receive third-line or later CAR-T therapy. The CS does not describe the subsequent treatments, but the company argue that the costs of subsequent treatments would be similar for patients who receive axi-cel and liso-cel (CS section B.4.2.1). The company clarified in their FAC document that epcoritamab (TA954), glofitamab (TA927) and loncastuximab tesirine (TA947) are recommended by NICE for use after two or more systemic treatments (3L+) and the recommendation for pola-BR (TA649) is not limited by treatment line. Thus, these treatment options could be given after 3L+ liso-cel or axi-cel.

The EAG's clinical experts explained that around half of patients survive long-term following CAR-T therapy. Those who relapse after an initial response would likely be offered bispecific antibody therapies or, if necessary, antibody-drug conjugates, or salvage chemotherapy (as per the NICE scope; Table 3). The experts noted that patients who relapse later, after 6-12 months, are more likely to respond to bispecific antibody therapy than those who relapse earlier. It is possible that the physical and social burden of subsequent treatments might be slightly less following liso-cel than axi-cel therapy given the more favourable safety profile of liso-cel, but the experts explained that immunosuppression and infections are also important factors affecting patient outcomes that are independent of the CAR-T therapy received. The experts agreed that, overall, the subsequent treatments received would be unlikely to differ systematically between patients who receive liso-cel or axi-cel.

2.3 EAG conclusion on the intervention and treatment pathway

The treatment pathway is appropriate and consistent with National Health Service (NHS) clinical practice, and similar for liso-cel and axi-cel (apart from liso-cel having a lower dose of cyclophosphamide lymphodepleting therapy than axi-cel which the EAG's clinical experts did not consider to be a concern for the cost comparison). There is a discrepancy between the doses of liso-cel used in the pivotal clinical study and that used in clinical practice, but this is unlikely to substantively compromise the generalisability of the study dosing to NHS clinical practice. Bridging therapy and

subsequent treatments are heterogeneous, reflecting the patient's condition and prior therapies but, overall, the EAG's clinical experts considered that the choice of regimens for these, and prognosis associated with them, would not differ systematically between liso-cel and axi-cel.

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

The intervention, comparator, and outcomes in the CS are consistent with the NICE scope and appropriate (see Table 3 below). Below (section 3.1) we summarise key points relating to the relevance of the company's decision problem population.

3.1 Population

The UK Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for liso-cel covers relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and grade 3 follicular lymphoma (FL3B).[8]

The company's decision problem population is narrower than the NICE scope, specifically focusing on patients suitable for CAR-T therapy (Table 3). This is appropriate as it matches the population for which the comparator therapy (axi-cel) was assessed (TA872)[1] and is within the company's marketing authorisation. The decision problem population is consistent with the NICE scope by excluding people who have FL3B (for which there are no NICE-recommended 3L+ comparator therapies relevant to a cost comparison).

The population for which the company have provided clinical evidence differs from the NICE scope by including DLBCL transformed from follicular lymphoma (tFL), DLBCL transformed from indolent non-Hodgkin lymphoma (tiNHL), and high-grade lymphoma (HGL) which are not specified in the NICE scope. The CS does not discuss these deviations from the scope. However, the EAG's clinical experts agreed that the inclusion of these lymphoma subtypes is clinically appropriate for a cost comparison analysis, given that the comparator appraisal TA872[1] followed a similar approach (although the classification of lymphoma subtypes has changed[9] and is therefore not identical between the liso-cel and axi-cel studies).

The NICE scope specifies the lymphoma types to be included in this appraisal as DLBCL or PMBCL, but the company have grouped these together, alongside the other LBCL subtypes noted above, in their decision problem population. The EAG's clinical experts agreed that grouping PMBCL, DLBCL, and the other lymphoma

subtypes together is appropriate in the comparison of liso-cel against axi-cel, as summarised in Table 2.

Table 2 Types of large B-cell lymphoma (LBCL) included by the company

Subtype	Summary and EAG experts' comments
Diffuse large B-cell lymphoma (DLBCL) (not otherwise specified)	The most frequent type of large B-cell or non-Hodgkin's lymphoma. An aggressive disease with heterogeneous prognosis (CS Table 3).
Primary mediastinal B-cell lymphoma (PMBCL)	Relatively rare compared to DLBCL. A generally fast-growing disease affecting specific anatomical sites, often in younger, and often female, patients (CS Table 3). The company argue that DLBCL is considered generalisable to PMBCL (CS section B.1.3). The EAG's clinical experts agreed, noting that those who have PMBCL would follow a similar treatment pathway to DLBCL.
Transformed follicular lymphoma (tFL)	Not described in the CS. A progression from follicular lymphoma, reflecting aggressive disease which the EAG's clinical experts considered would have heterogeneous but broadly similar prognosis and treatment to that of DLBCL.
Transformed indolent non-Hodgkin lymphoma (tiNHL)	Not described in the CS. A progression of non-Hodgkin lymphoma from an initial indolent state, reflecting aggressive disease which the EAG's clinical experts considered would have heterogeneous but broadly similar prognosis and treatment to that of DLBCL.
High-grade lymphoma (HGL)	Not described in the CS. HGL has a poorer prognosis than the other lymphoma subtypes, often rapidly progressing[9] but the EAG's clinical experts considered that in the context of a non-inferiority analysis it is appropriate for the company to include HGL.

Subtype	Summary and EAG experts' comments
	The classification and diagnosis of HGL has changed recently[9] which has implications for the comparability of the liso-cel and axi-cel studies (see section 4.3.3 below).
Follicular lymphoma grade 3B (FL3B)	Not described in the CS. A subtype with variable but generally more favourable prognosis than the other subtypes.[10] FL3B has no NICE-recommended relevant comparator therapy but is of negligible numeric importance in the CS (1.9% of the company efficacy analysis set). The company have excluded FL3B from their indirect treatment comparison of liso-cel against axi-cel (CS Tables 31 and 24) which the EAG agree is appropriate.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with relapsed or refractory DLBCL or PMBCL, after two or more lines of systemic therapy	Adult patients with R/R DLBCL or PMBCL after two or more systemic therapies who are suitable to receive CAR-T cell therapy	The target population for liso-cel in this submission is narrower than the NICE final scope as it focuses on a targeted population of those suitable to receive CAR T at 3L+. The target population is however in line with the patient population in which axi-cel (the main comparator) is routinely prescribed in clinical practice. This positioning represents a subpopulation of the licensed indication for liso-	Agree with the company that the population suitable for 3L+ CAR T-cell therapy is appropriate for the decision problem. However, the clinical evidence provided by the company includes lymphoma subtypes (tFL, tiNHL, FL3B) not specified in the NICE scope and the company have grouped together patients with DLBCL and PMBCL in their analyses. As explained above (section 3.1), the EAG's clinical experts agreed with the inclusion of these lymphoma subtypes and the

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			cel, which excludes patients with R/R FL3B.	pooling of PMBCL with DLBCL.
Intervention	Lisocabtagene maraleucel	Lisocabtagene maraleucel	In line with NICE final scope	Agree with the company
Comparators	The main relevant comparator is: ● Axicabtagene ciloleucel Other comparators are: ● Salvage chemotherapy combination regimens with or without rituximab, including: ● DHAP (dexamethasone, cytarabine, cisplatin) ● ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ● GDP (gemcitabine, dexamethasone, cisplatin)	Axicabtagene ciloleucel	The target population for liso-cel is adult patients with R/R DLBCL or PMBCL after two or more systemic therapies who are suitable to receive CAR-T cell therapy. Axi-cel represents the most relevant comparator to liso-cel in UK clinical practice for the following reasons: ● Both liso-cel and axi-cel are autologous CD19	The EAG's three clinical experts agreed that axi-cel is the most relevant comparator as it is the only CAR T-cell therapy listed in the NICE scope, has a similar mechanism of action to liso-cel, and is embedded in NHS clinical practice. The EAG do not agree with the company's statement that "patients who are suitable for CAR-T cell therapy would

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	● GemOX (gemcitabine and oxaliplatin) ● ICE (ifosfamide, carboplatin, etoposide) ● IVE (ifosfamide, epirubicin and etoposide) ● Polatuzumab vedotin with rituximab and bendamustine (only when stem cell transplantation is not suitable) ● Loncastuximab tesirine (if previously had polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) ● Glofitamab		directed CAR-T cell therapies with similar mechanisms of action ● Axi-cel is the established SOC in UK clinical practice in the targeted population and is prescribed to the vast majority of patients with R/R DLBCL and PMBCL at 3L+ who are suitable for CAR-T cell therapy ● Liso-cel and axi-cel offer comparable efficacy in the target population. This is supported by a MAIC, RWE studies and UK CAR T Experts' feedback.	likely only receive treatment with CAR-T cell therapy, rather than an alternative therapy". This is because not all patients eligible for a liso-cel infusion receive it. However, the proportion suitable for but unable to receive CAR T-cell therapy in the company studies is relatively small and the EAG's clinical experts did not believe that the prognosis or treatments received by these patients would differ between CAR T-cell products.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	● Epcoritamab (if previously had polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory DLBCL		Additionally, patients who are suitable for CAR-T cell therapy would likely only receive treatment with CAR-T cell therapy, rather than an alternative therapy. Therefore, the only relevant comparator to liso-cel in the CAR T suitable population at 3L+ is axi-cel.	
Outcomes	● Progression-free survival ● Overall survival ● Response rates, including time to next treatment and duration of response ● Adverse effects of treatment	● Progression-free survival ● Overall survival ● Response rates, including time to next treatment and duration of response	CS states the outcomes are in line with the final NICE scope	The company have included all outcomes specified in the NICE scope that were included in the NICE appraisal of the comparator, axi-cel (TA872[1]), as is required for a cost comparison, namely progression-free survival,

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	● Health-related quality of life	● Adverse effects of treatment ● Health-related quality of life		overall survival, and adverse events.
Economic analysis	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect	● The cost comparison of liso-cel versus axi-cel has been evaluated, in line with the NICE reference case ● Costs were considered from a PSS perspective ● A patient access scheme for liso-cel was included in the analysis	Liso-cel is considered to meet all the criteria for a cost-comparison appraisal, enabling the economic assessment to be conducted through a cost-comparison analysis.	NICE's criteria for economic analysis have been followed. The company assume similar clinical efficacy of liso-cel and axi-cel and that there are no long-term costs beyond intravenous immunoglobulin (IVIg) therapy and therefore no formal time horizon was considered (CS section B.4.2.1).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	any differences in costs or outcomes between the technologies being compared			
Subgroups	If evidence allows, the following subgroups will be considered: ● Type of lymphoma (DLBCL, PMBCL) ● Grade of lymphoma ● Number of previous treatments ● Previous stem cell transplant	Subgroups from the pivotal TRANSCEND trial were explored and are presented in the CS	Subgroups were explored based on available data.	Subgroup analysis results in the CS (CS Figure 9) are for ORR only, not survival outcomes. Some subgroup results are reported in the 2019 clinical study report (CSR) Addendum, but these are not for relevant data cuts and dose levels of liso-cel, or have very small sample sizes.

3L+, third-line or later; CAR-T, T-cell chimeric antigen receptor; CSR, clinical study report; HSCT, haematopoietic stem cell transplant; DLBCL, diffuse large B-cell lymphoma; FL3B, follicular lymphoma grade 3B; MAIC, matching-adjusted indirect comparison; ORR, objective response rate; PMBCL, primary mediastinal B-cell lymphoma; PSS, personal social services; R/R, relapsed or refractory; RWE, real-word evidence; SOC, standard of care; tFL, transformed follicular lymphoma; tiNHL, transformed indolent non-Hodgkin lymphoma.

3.2 EAG conclusion on the company's decision problem

The decision problem is narrower than the NICE scope which is appropriate to align with the population included in the appraisal, i.e. patients suitable for CAR-T therapy at third-line or later. The clinical evidence provided by the company includes lymphoma subtypes that are not specified in the NICE scope but the EAG's clinical experts considered this appropriate for the present cost comparison analysis. The EAG and our clinical experts agree that the company's selection of axi-cel as the sole comparator is appropriate.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

The company carried out a systematic literature review (SLR) in April 2019 and updated it in February 2021 and September 2025. Referred to as the clinical SLR, it aimed to identify all evidence for third-line or later (3L+) treatments for large B-cell lymphoma (CS Appendix D for the 2025 update and separate company reports for the original SLR and 2021 update).

The conduct of the clinical SLR was appropriate: the searches are likely to have retrieved all relevant literature, and the selection criteria match the appraisal decision problem. The searches were designed to include randomised controlled trials (RCTs) and would likely have identified them had there been any. The EAG's clinical experts were not aware of any relevant RCTs.

The company identified four single-arm studies that provide evidence for liso-cel in patients with relapsed/refractory LBCL at 3L+ (CS section B.3.2).

4.2 Critique of studies of lisocabtagene maraleucel (liso-cel)

Most of the information about the studies is reported in the CS and Appendices, although some of the study information is in a separate report about the company's indirect treatment comparison which we refer to as the MAIC Report.

4.2.1 Overview of the studies

The four included studies (TRANSCEND[3] (NCT02631044), TRANSCENDWORLD (NCT03484702), GC-LTFU-001 (NCT03435796) and OUTREACH[11] (NCT03744676) are all prospective, single-arm, open-label company studies evaluating liso-cel in the relevant LBCL population. Only TRANSCEND, with long term follow-up data from GC-LTFU-001, informs the main comparative evidence for the clinical efficacy and safety of liso-cel which is provided by an indirect treatment comparison (ITC) (section 4.3 below). We discuss the TRANSCEND and GC-LTFU-001 studies in section 4.2.2 below.

TRANSCENDWORLD and OUTREACH are completed studies providing supportive clinical efficacy and safety data, with OUTREACH providing evidence for liso-cel in

an outpatient setting. They are of relatively short duration (median follow-up: TRANSCENDWORLD 15.8 months; OUTREACH 10.6 months) and have relatively small sample sizes (TRANSCENDWORLD N=36; OUTREACH outpatients N=57, inpatients N=25) compared to the TRANSCEND study. They do not inform the company's ITC or economic conclusions.

4.2.2 TRANSCEND and GC-LTFU-001 studies

The key characteristics of TRANSCEND and GC-LTFU-001 are summarised in **Error! Reference source not found.**, with further details on the population, p osology, and the analysis sets below.

Table 4 Overview of TRANSCEND and GC-LTFU-001

Characteristic	TRANSCEND	GC-LTFU-001
Study identifier	NCT02631044	NCT03435796
Role in the evaluation	Main source of clinical efficacy and safety data for liso-cel (section 4.2.5 below); contributes the liso-cel data to the company's ITC (section 4.3 below)	Long-term follow up study for up to 15 years for participants who continued from TRANSCEND and TRANSCENDWORLD; informs OS and long-term safety for the economic analysis (for participants originally in TRANSCEND)
Relevant cohort	"DLBCL Cohort" (section 4.2.2.3 below) including dose levels 1 and 2 (for explanation of dose levels see section 4.2.2.2).	Participants with LBCL including dose levels 1 and 2.
Sample size (of relevant cohort)	Efficacy Set N=216; Treated Set (safety) N=229 Both based on the DLBCL cohort - see also Table 5 and section 4.2.2.3 below.	N=74 from TRANSCEND
Duration	Completed. January 2016-May 2024	Ongoing. July 2018 – November 2036
Data cut	28 September 2021	31 January 2024
Median follow up	[redacted] months (range: [redacted] months)	[redacted] months (range: [redacted] months)

Characteristic	TRANSCEND	GC-LTFU-001
Outcomes used in the ITC	PFS, OS, adverse events	OS, long term adverse events
Source: CS sections B.3.2, B.3.6.1.1, and CS Table 6; CS Appendix M; Table 4 in TRANSCEND CSR 2024. Abbreviations: CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; ITC, indirect treatment comparison; LBCL, large B-cell lymphoma; OS, overall survival, PFS, progression free survival.		

4.2.2.1 Study population

TRANSCEND was a multicentre study conducted in the US. Participant baseline characteristics for TRANSCEND are reported for the Treated Set in CS Table 13 and for the Efficacy Set in Table 6 of the company MAIC report. The EAG's clinical experts considered the TRANSCEND study population to be generally reflective of patients seen in NHS clinical practice and similar to other UK real-world evidence cohorts of patients with relapsed or refractory LBCL, e.g. Kuhnl et al. 2022.[12]

4.2.2.2 Study posology

TRANSCEND clinical efficacy results in the CS are reported for participants who received a single or double infusion of liso-cel dose level 1 (DL1) or a single infusion of dose level 2 (DL2). The single infusions of DL1 and DL2 are within the target dose range according to the Summary of Product Characteristics13 (for explanation of the dose levels see section 2.2.2 above). The double infusion of DL1 is not within the marketing authorisation but was only received by [redacted] participants in TRANSCEND (CS Table 7), so the company do not consider this a threat to generalisability of the study results (CS section B.3.3.1) and the EAG agree. However, the EAG's clinical experts explained that in NHS practice only a single infusion of DL2 would likely be used for 3L+ (i.e. the same dose as currently used at second line). The experts viewed that this difference would not favour liso-cel in terms of clinical efficacy in TRANSCEND since a single infusion of DL1 in the study is a lower dose than would be used in practice, whilst the double infusion of DL1 would give the same total dose as expected in clinical practice. There is a possibility that the lower dose regimen DL1 in TRANSCEND might lead to underestimation of adverse events, but this

seems unlikely given that most of the participants in the analysis (78%) had a single infusion of DL2 which aligns with clinical practice. On balance, the EAG's clinical experts believed the posology in TRANSCEND would not substantively preclude generalisability of the efficacy or safety results to clinical practice.

In summary, there are some deviations of the dosing regimens in TRANSCEND from both the marketing authorisation and anticipated clinical practice but the EAG's clinical experts did not expect these would compromise the generalisability of the study results.

4.2.2.3 Analysis sets

The company provided three analysis sets for TRANSCEND, two of which include GC-LTFU-001 data (CS Table 9) that are relevant to the population being appraised (summarised in Table 5 below). These analysis sets are based on the TRANSCEND "DLBCL Cohort" which consists of participants with the lymphoma subtypes DLBCL, HGL, PMBCL and FL3B (CS Table 10) (for a description of the lymphoma subtypes see Table 2 above). Although the analysis sets contain participants with FL3B, these only represent 1.7% of the sample (CS Table 13) and the EAG's clinical experts did not expect them to be treated differently to the other patients.

Table 5 TRANSCEND and GC-LTFU-001 analysis sets used in the CS

Analysis set (all derived from the "DLBCL cohort")	**Sample size**	**How used in** the **CS**
Leukapheresis Set, DL1+DL2	N=[redacted]	Mortality data (CS Table 41 and CS Appendix Table 48)
Treated Set, DL1+DL2	N=229	Participant baseline characteristics (CS Table 13), patient disposition summary (CS Table 10), all treatment-emergent adverse events except deaths (CS sections B.3.10.1 to B.3.10.1.2).
Treated Set, All doses	N=[redacted]	Longer-term adverse events, including data from the long term follow up study GC-LTFU-001 for participants who continued from TRANSCEND (CS Appendix J.5.2).

Analysis set (all derived from the "DLBCL cohort")	**Sample size**	**How used in** the **CS**
Efficacy Set, DL1+DL2	N=216	Efficacy results (CS sections B.3.6.1.1 to B.3.6.1.3) and company indirect treatment comparison (CS section B.3.9) Long term OS results (includes data from the long term follow up study GC-LTFU-001 for participants who continued from TRANSCEND; CS section B.3.6.1.3)
Source: CS Tables 8, 9, and 11; Clarification Responses A1b and A1c. Abbreviations: DL1, dose level 1; DL2, dose level 2 (for explanation see section 2.2.2); OS, overall survival.		

The Efficacy Set differs from the Treated Set because it carries the additional requirement of an eligibility criterion in TRANSCEND to have PET (positron emission tomography)-positive disease before administering liso-cel. The EAG's clinical experts described different timing of PET scans to assess disease status in their practices. One expert said that they would carry out PET scans between bridging and CAR-T therapy while another expert said the scans may be done earlier. Overall, the experts agreed that the analysis sets in TRANSCEND are generalisable to the treatment pathway for patients initiating CAR-T therapy in clinical practice.

Both the Treated Set (N=229) and the Efficacy Set (N=216) do not include participants who, after receiving leukapheresis, were not treated with liso-cel, nor do they include participants who received a non-conforming product (CS Table 9). Therefore, the efficacy results and subsequent analyses are not based on all patients in the decision problem population. However, the EAG's clinical experts considered the analysis populations appropriate for a cost comparison as the prognosis and subsequent treatment of excluded patients, although heterogeneous, would not be expected to differ systematically between patients on liso-cel and axi-cel pathways. The experts explained that those eligible for but unable to receive CAR-T therapy at third-line or later have poor prognosis, with relatively high mortality resulting from progressive disease or infection. Surviving patients would be offered bispecific antibody therapies, antibody-drug conjugates, or salvage chemotherapy (as per the NICE scope; Table 3), depending on the patient's previous treatment

history and their ability to tolerate the therapy. If available, patients might be offered an opportunity to join a clinical trial.

4.2.3 Risk of bias assessment

The company performed risk of bias assessments using the Downs and Black checklist,[14] (CS Appendix 12) but only provided a risk of bias interpretation for TRANSCEND which they assessed to be at low risk of bias (CS section B.3.5). However, the EAG consider that as TRANSCEND, OUTREACH, TRANSCENDWORLD, and GC-LTFU-001 are open-label, single-arm studies they each have a high risk of bias.

4.2.4 EAG conclusion on the studies of liso-cel

The primary study of liso-cel, TRANSCEND, is a single-arm study whose main role in the CS is to inform an indirect treatment comparison to enable comparison of liso-cel against axi-cel. Longer-term data from TRANSCEND are provided by a follow-on study, GC-LTFU-001, which also informs the ITC. The CS briefly reports results from two other studies, TRANSCENDWORLD and OUTREACH but these have substantially shorter follow-up. As the TRANSCENDWORLD and OUTREACH studies do not identify any additional clinical efficacy or safety signals they are not included in this report.

We note that the OUTREACH study provides immature evidence on the use of liso-cel in an outpatient setting. One of the EAG's clinical experts explained that in their practice they will shortly begin treating a patient with liso-cel in an outpatient setting, suggesting that when data become more mature an appraisal of outpatient use of liso-cel may be appropriate. However, the company have not included outpatient administration of liso-cel in the present cost comparison.

4.2.5 Key clinical efficacy results of the intervention studies

Below we summarise results from TRANSCEND for outcomes that are relevant to the current cost comparison, i.e. PFS, OS and adverse events. Results for other outcomes including response rates and health-related quality of life can be seen in CS section B.3.6.1. There are some limitations to the results reported below given that there was no comparator in TRANSCEND against which to assess comparative clinical efficacy and safety, and the statistical power calculation in TRANSCEND

applies to the achievement of ORR and complete response rather than the survival outcomes.

4.2.5.1 Progression free survival (PFS)

Table 6 below presents the PFS results from the TRANSCEND study.

Table 6 PFS results for liso-cel, TRANSCEND Efficacy Set DL1+DL2 (N=216)

Analysis	Median follow-up, months	Median PFS, months (95% CI)
Assessed by IRC; EMA censoring rules	[redacted]	[redacted]
Assessed by INV; EMA censoring rules	[redacted]	[redacted]
Assessed by INV; FDA censoring rules	[redacted]	[redacted]
Source: CS section B.3.6.1.3, CS Table 20, CS Appendix Table 41, CS Table 35; Table 16 in company MAIC Report. Abbreviations: CI, confidence interval; DL, dose level; EMA, European Medicines Agency; FDA, US Food and Drug Administration; INV, investigator; IRC, Independent Review Committee; PFS, progression-free survival.		

The [redacted] median PFS ([redacted] months) was with EMA censoring rules and independent review committee (IRC) assessment. The analyses based on investigator (INV) assessment show a slightly [redacted] median PFS, but the confidence intervals overlap, so the differences may not be meaningful. The EMA censoring rules give fewer reasons to censor a patient than the FDA rules; that is, under EMA rules patients are not censored when they begin new anti-cancer treatments, receive a transplant, or have missed two or more scheduled disease assessments (CS Table 14). For participants who were censored under the FDA rule for starting a new anti-cancer treatment, the company provided a list of the new anti-cancer therapies and the censoring date (Clarification Response A2).

4.2.5.2 Overall survival (OS)

The OS results for TRANSCEND include data from the latest data cut (31 January 2024) of the long-term follow-up study GC-LTFU-001.

At a median follow-up of [redacted] months, the median overall survival for the Efficacy Set, DL1+DL2 (N=216) was [redacted] months (95% CI [redacted]) (CS Table 21; TRANSCEND clinical study report 2024; MAIC Report Table 8).

There is a distinct cluster of censoring at 24 months for both PFS (CS Figure 7) and for OS (CS Figure 8) and the company explained this was due to censoring participants from TRANSCEND who did not enter the GC-LTFU-001 study (Clarification Response A1c).

4.2.5.3 Clinical interpretation of the TRANSCEND survival outcomes

As a single-arm study, there is no comparator or control arm in TRANSCEND to contextualise the PFS and OS results, nor are there any predefined criteria or thresholds of success for achieving clinically important PFS or OS. All three of the EAG's clinical experts interpreted the results as clinically meaningful. One expert suggested that axi-cel, as the current standard of care for patients eligible for CAR-T therapy, would be the benchmark and as such the company's indirect treatment comparison reported in section 4.3 below provides relevant comparative clinical efficacy evidence. The other experts commented that the OS in TRANSCEND is longer than that seen in trials of chemotherapies where overall survival was only a few months and is at least as good as overall survival seen after receiving bispecific antibodies.

4.2.6 Key safety results of the intervention studies

In TRANSCEND, treatment emergent adverse events (TEAEs), defined as adverse events occurring ≥90 days after the last liso-cel dose, are reported for the Treated Set dose levels DL1+DL2 (N=229) (data cut 28 September 2021). The post-treatment-emergent adverse events (post-TEAEs), defined as adverse events occurring ≥91 days after the last liso-cel dose, or earlier if the patient started another cancer treatment or received liso-cel again before day 91, are reported for the Treated Set, all dose levels (N=[redacted]), and include data from the long-term follow-up study GC-LTFU-001 (data cut 31 January 2024). Post-TEAEs were reported to assess long-term toxicity and viral vector safety for up to 15 years post-last dose of liso-cel in accordance with health authority guidance on viral vector-based gene therapy products (TRANSCEND 2024 CSR page 12).

[redacted] participants [redacted] experienced any grade of TEAE; [redacted] experienced Grade ≥3 TEAEs of which the most common were cytopenias; and [redacted] experienced serious adverse events (CS Tables 38 and 40).

The most frequent treatment-emergent adverse events of special interest (AESIs) were prolonged cytopenia ([redacted] %), followed by cytokine release syndrome (CRS) ([redacted] %), neurological toxicity ([redacted] %), hypogammaglobulinaemia ([redacted] %) and Grade ≥3 infections ([redacted] %) (CS Table 38). CRS and neurotoxicity are known toxicities associated with CAR-T therapies and the company provide further details in CS section B.3.10.1.2 and the study clinical study report (CSR). The EAG's clinical experts advised that cardiovascular events may also be relevant, although their occurrence would likely be the same for liso-cel and axi-cel. The experts also commented that cardiovascular toxicity and second primary malignancies would most likely arise from other aspects of the treatment pathway (e.g. prior chemotherapy) rather than from the CAR-T therapy, whilst immunosuppression, prior treatment, and CAR-T therapy can all contribute to the development of hypogammaglobulinaemia.

Post-treatment-emergent adverse events were less frequent than treatment-emergent adverse events (CS Appendix Table 49) and no new safety concerns were identified (CS Appendix J.5.2). The EAG's clinical experts commented that they would not expect to see any substantive differences in adverse events between liso-cel and axi-cel in the longer term.

Deaths in TRANSCEND are reported for both the TEAE and post-TEAE periods for the Leukapheresis Set (CS section B.3.10.1.3, CS Table 41, and CS Appendix Table 48). This is appropriate because the Leukapheresis Set includes all the patients in the decision problem population. Most deaths were due to disease progression, which the EAG's clinical experts confirmed reflects clinical practice. The experts explained that after 12 months post CAR-T therapy, late events such as infection due to toxicity can cause death, but overall disease progression is the leading cause of death.

4.2.7 Pairwise meta-analysis of intervention studies

A pairwise meta-analysis was not feasible because only single-arm studies were available for liso-cel and axi-cel. An indirect treatment comparison was therefore conducted (section 4.3).

4.3 Critique of the indirect treatment comparison (MAIC)

The company used an unanchored matching-adjusted indirect comparison (MAIC) to compare the clinical effectiveness and safety outcomes for liso-cel (TRANSCEND study) against those for axi-cel (ZUMA-1 study). The MAIC methods and results are described in CS section B.3.9, with full details given in a separate report provided by the company, henceforth referred to as the MAIC Report.

4.3.1 Rationale for the MAIC

Only single-arm studies of liso-cel and axi-cel are available (i.e. with no common comparator arm), and therefore the EAG agree that an unanchored MAIC is appropriate. Unanchored MAIC is subject to the limitations that the results should be considered observational in nature due to the lack of randomisation, and a strong assumption is required that all prognostic factors and effect modifiers have been identified and are balanced between the studies.[15] The company acknowledge that it is virtually impossible to adjust for all possible factors that may differ between studies (CS section B.3.9.4). We agree that despite these limitations MAIC is the analytical approach best suited to the structure of the available evidence.

4.3.2 Identification, selection and feasibility assessment of studies for the MAIC

The company report their clinical SLR in CS Appendix D and Appendix B of a standalone company document. A lack of transparency in reporting the identification and selection of comparator (axi-cel) studies for inclusion in the MAIC was resolved by the company in Clarification Response A3. Following this clarification, and consultation with our three clinical experts, the EAG believe that all relevant studies that could be included in an indirect treatment comparison have been identified. These are the TRANSCEND study of liso-cel[2, 3] and the ZUMA-1 study of axi-cel[4, 5] (CS section B.3.9.1). ZUMA-1 was the primary study that informed NICE's appraisal of axi-cel after two or more systemic therapies (TA872).[1] The EAG's clinical experts

were not aware of any other studies or UK real-world evidence cohorts for liso-cel or axi-cel in the 3L+ setting of relapsed or refractory LBCL that could inform an indirect treatment comparison.

4.3.3 Clinical heterogeneity assessment and identification of clinical factors for potential matching or adjustment

The company explored differences in eligibility criteria and population baseline characteristics between the TRANSCEND and ZUMA-1 studies (CS section B.3.9.3 and MAIC Report section 4.2.2).

There are differences between TRANSCEND and ZUMA-1 in the way that LBCL histology was reported (CS Table 29), which reflects a change in how lymphoma subtypes have been classified since the ZUMA-1 study was initiated (see section 3.1 above). To address these differences the company re-classified the lymphoma subtypes such that DLBCL (not otherwise specified), HGL, and tiNHL from TRANSCEND were grouped together in “DLBCL” for comparison to the “DLBCL” category in ZUMA-1 (MAIC Report Table 5). The resulting subtype categories are as shown in CS Table 30. The company also re-classified several other clinical variables as noted in MAIC Report Table 5. The EAG’s clinical experts noted that the different lymphoma subtype classifications in the studies would inevitably contribute to heterogeneity in outcomes but considered the company’s approach of re-classifying the lymphoma subtypes and other clinical variables to optimise comparability of the studies to be clinically appropriate.

4.3.3.1 Identification of factors for potential matching or adjustment

Relevant clinical factors for adjustment in a MAIC analysis (i.e. prognostic factors and effect modifiers) were identified by targeted literature searches (not described further) which identified 37 potential factors relating to efficacy outcomes (MAIC Report section 8.1.1) and 23 potential factors relating to safety outcomes (MAIC Report section 8.2).

A ranking process involving five partially-blinded clinical experts with diverse experience (not identified but each was from a different country) was used to reach a final list of clinical factors for potential adjustment in the MAIC. The process included multiple steps and a random forest regression analysis to account for the strength of

association between the clinical factors and each efficacy outcome (MAIC Report sections 8.1. to 8.3). An abbreviated ranking process, without the strength of association assessment, was used to prioritise the potential clinical factors relevant to safety outcomes (i.e. for adverse events of special interest, AESI) (MAIC Report section 8.2).

Ranking identified 24 clinical factors for clinical efficacy outcomes, of which 20 were reported as available for comparison between TRANSCEND and ZUMA-1 (MAIC Report Table 19), and 16 clinical factors for AESI of which 12 were reported as available for comparison between the studies (MAIC Report Table 20). The company do not specify whether the clinical factors are prognostic factors and/or effect modifiers, but the EAG's three clinical experts believed that no important prognostic factors or effect modifiers for clinical efficacy or safety are missing from these lists.

4.3.3.2 Matching and adjustment process

The company followed a two-stage approach, matching and adjustment, to minimise the heterogeneity in characteristics of the TRANSCEND and ZUMA-1 studies and optimise their comparability.

4.3.3.2.1 Matching

The company removed any patients from the TRANSCEND individual participant data (IPD) set if they did not meet the eligibility criteria for ZUMA-1. The five factors removed were disease histology, prior allogenic haematologic stem cell transplant (allo-HSCT), ECOG performance score (ECOG PS) 2, central nervous system (CNS) involvement, and receipt of bridging therapy (MAIC Report Table 11). For safety outcomes the same factors except disease histology were removed from TRANSCEND (as explained in the company's FAC document, disease histology was excluded as it was not identified in the targeted literature review or suggested by the clinical experts consulted).

The EAG agree that removing patients from TRANSCEND is a pragmatic way to match the studies on eligibility criteria. However, this means that bridging therapy, which is used in NHS clinical practice, was removed from the primary analysis because it was not included in ZUMA-1. The experts suggested that ZUMA-1 could therefore have selected patients with less aggressive disease, although (as noted in

section 2.2.4 above) receipt of bridging therapy would not necessarily lead to a systematic difference in patient prognosis between the studies.

The EAG's clinical experts commented that, ideally, a more realistic comparison would be to match the ZUMA-1 characteristics to the TRANSCEND study, as TRANSCEND was less restrictive in its eligibility criteria and a closer reflection of UK clinical practice. However, this was not feasible using the MAIC due to the granularity of the available data which dictate the direction of matching (IPD for TRANSCEND, summary-level data for ZUMA-1).

To address these limitations, for each outcome the company conducted a primary analysis that excluded patients from TRANSCEND who did not meet the five ZUMA-1 eligibility criteria as mentioned above, and sensitivity analyses which included patients in TRANSCEND who had received bridging therapy (the sensitivity analyses also included different adjustment factors as described in section 4.3.3.2.2 below). The EAG's clinical experts considered the sensitivity analyses for exploring the influence of bridging therapy appropriate. Sensitivity analyses were not conducted for safety outcomes, but the CS and MAIC Report do not explain why not.

4.3.3.2.2 Adjustment

Patients who remained in the TRANSCEND study IPD set after the matching phase were weighted using a method-of moments propensity score algorithm to balance the clinical factors between studies (MAIC Report section 4.2.4). The EAG agree that this is an appropriate adjustment method.

For PFS and OS analysis, of the 20 'available' clinical factors identified for consideration (section 4.3.3.1 above), five factors were used in matching as described above (section 4.3.3.2.1), whilst footnote 'c' in MAIC Report Table 19 indicates two factors (cell of origin, and double/triple hit or double expressor) were not available in the ZUMA-1 efficacy set (but were available in the safety set). The remaining 13 factors were adjusted in the MAIC efficacy analyses. Six of these factors were adjusted in the primary analysis (tumour burden, International Prognostic Index (IPI) score, relapsed or refractory to the last therapy, bulky disease, age [for OS only], creatinine clearance [for PFS only]) and eight were adjusted in sensitivity analyses (prior autologous HSCT, disease stage, extranodal disease,

number of prior therapies, sex, absolute lymphocyte count, and left ventricular ejection fraction [LVEF], creatinine clearance [for OS only], age [for PFS only]) (MAIC Report Table 12). The EAG's clinical experts agreed that all key factors had been included across the primary analysis and two sensitivity analyses for each outcome. The second sensitivity analysis included the largest number of adjustment factors (all 13).

For safety analysis, MAIC Report section 8.3.1 mentions 12 clinical factors were available for comparison (section 4.3.3.1 above). The CS and MAIC Report contain discrepancies in the numbers of factors included/excluded but the company clarified in their FAC document: "Bone marrow involvement was excluded from the safety MAIC. Of the remaining eleven factors, two were not included within the base case analysis (age and prior auto-HSCT), four were matched as described above (section 4.3.3.2.1), and the remaining five were adjusted in the base case analysis (MAIC Report section 4.3.1.2). A sensitivity analysis was conducted including all eleven factors." However, the EAG note that no results of sensitivity analyses for the MAIC safety outcomes have been reported.

4.3.3.2.3 Outcome of the matching and adjustment process

Comparison of clinical factors before and after adjustment suggests that the second sensitivity analysis achieved the best matching for PFS and OS (CS Table 34; MAIC Report Tables 25 and 26). The primary analysis achieved relatively poor matching compared to the sensitivity analyses, having the highest proportions of clinical factors with SMD ≥0.2 (around [redacted] %) after matching (CS section B.3.9.5 and MAIC Report section 5.1.1.1), and the lowest ESS values (PFS [redacted], OS [redacted]) (CS Tables 35 and 36), together with some high patient weights (MAIC Report Figures 20 to 25). The matching between TRANSCEND and ZUMA-1 was generally good for the safety outcomes, when judged on patient weights (MAIC Report Figure 26) and SMD with most characteristics having SMD<0.2 (MAIC Report Table 29), but matching was relatively poor for patient age (SMD [redacted]) and overall ESS was relatively [redacted] ([redacted] for the Treated Set in CS Table 37 and [redacted] for the Efficacy Set in MAIC Report Table 29).

4.3.4 Risk of bias assessment for studies included in the MAIC

The company used the Downs and Black checklist[14] for critically appraising the TRANSCEND and ZUMA-1 studies (CS Table 15 and CS Appendix Table 11). The checklist includes 13 questions about internal validity (i.e. risk of bias), seven of which are relevant to single-arm studies, as well as questions about external validity, reporting, and statistical power (which are not typically part of a risk of bias assessment). The company have not provided risk of bias judgements for the individual checklist questions and instead leave the output as a series of yes/no/unclear responses with no further interpretation provided. Overall, as noted in section 4.2.3 above, the company judged there to be a low risk of bias in TRANSCEND (CS section B.3.5), but have not provided an opinion on the risk of bias in ZUMA-1.

The EAG do not agree with the company's critical appraisal approach, which lacks transparency. We consider both the TRANSCEND and ZUMA-1 studies to have an inherently high risk of bias due to being uncontrolled and open-label studies.

4.3.5 Data inputs to the MAIC

The company used IPD from TRANSCEND and its long-term extension study GC-LTFU-001 for liso-cel and summary-level data from ZUMA-1 for axi-cel. The liso-cel data are from the DLBCL Efficacy Set and the DLBCL Safety Set of TRANSCEND which included dose levels DL1 and DL2 as single infusions and DL1 as a double infusion (only DL2 is likely to be used in NHS clinical practice – see section 4.2.2.2 above). For survival outcomes from TRANSCEND the company used investigator assessments and Food and Drug Administration (FDA) censoring rules to ensure consistency with the analysis approach in ZUMA-1, which the EAG agree is appropriate.

Median follow-up for PFS was [redacted] months for liso-cel (TRANSCEND (28th September 2021 data cut) and 63.1 months for axi-cel (ZUMA-1; 11th August 2021 data cut). Median follow-up for OS was [redacted] months for liso-cel (TRANSCEND + GC-LTFU-001; 31st January 2024 data cut) and 63.1 months for axi-cel (ZUMA-1; 11th August 2021 data cut). For safety outcomes the median follow-up was [redacted]

months for liso-cel (the same data cut as for PFS) and 27.4 months for axi-cel (11th August 2018 data cut) (CS Table 27).

Overall, the EAG agree that the company have used the most appropriate of the available data inputs for the MAIC analyses.

4.3.6 Statistical methods for the MAIC

The company conducted an unanchored MAIC following the approach recommended in Decision Support Unit (DSU) Technical Support Document (TSD) 18 (TSD18).[15]

The statistical approach for the MAIC is described in MAIC Report section 4.2.5. Model suitability was assessed using the effective sample size (ESS), the distribution of patient weights, the change in value of clinical characteristics after the matching and adjustment steps, and the absolute value of the standardised mean difference (SMD) (MAIC Report section 4.2.6).

The company provided the statistical code in Clarification Response A6. The EAG were unable to verify the MAIC analysis since IPD from the TRANSCEND study are confidential. However, we did not identify any concerns from the statistical code.

The EAG agree that there is no evidence to suggest violation of the proportional hazards assumption, based on the results of log cumulative hazard plots and Grambsch-Therneau test results (Clarification Response A5).

In summary, we agree that the company have used an appropriate statistical approach, except for some lack of clarity around the safety analysis, but we note that matching and adjustment was not entirely successful at balancing the study populations in the primary analysis (see section 4.3.7 below).

4.3.7 Summary of the EAG's critique of the MAIC

The MAIC analyses were generally well conducted and appropriate, making best use of the available evidence, and likely capturing all known relevant prognostic factors and effect modifiers. However, there are several sources of heterogeneity in the MAIC results:

- The unanchored MAIC approach is inherently uncertain, being inferior to a randomised comparison (section 4.3.1)
- TRANSCEND was the more clinically relevant reference study but matching had to use ZUMA-1 as the reference due to limitations in the available data (section 4.3.3.2.1)
- Matching of the clinical factors in the liso-cel and axi-cel studies was not fully successful for all clinical efficacy analyses, being best for the second sensitivity analysis (section 4.3.3.2.3)
- The analysis of safety outcomes was less detailed than that of the clinical efficacy outcomes, with an abbreviated ranking process (section 4.3.3.1), and results of the sensitivity analysis (section 4.3.3.2.2) are not reported.
- The included studies have high risks of bias (section 4.3.4)
- The analysis population included several LBCL subtypes which had to be re-classified to ensure comparability between the studies (section 4.3.3)
- The dose regimens of liso-cel in the TRANSCEND study do not precisely align with the dosing expected to be used in clinical practice (section 4.3.5)
- No margins for clinical similarity, equivalence, or non-inferiority have been specified for the MAIC analysis and therefore the hypothesis that the efficacy and safety of liso-cel are at least similar to those for axi-cel, as required for a cost comparison,[16] cannot be verified statistically.
- The MAIC results reported below (section 4.4) should be interpreted with caution given these uncertainties.

4.4 MAIC results

4.4.1 Progression-free survival

CS Table 35 shows the PFS results for the primary analysis and both sensitivity analyses, compared to a naive comparison before matching and adjustment was applied. In all MAIC analyses the hazard ratio (range [redacted] to [redacted]) was [redacted] significant, with [redacted] confidence intervals [redacted]. The ESS was lowest for the primary analysis and ranged [redacted] to [redacted], compared to a sample size of N=216 for the starting DLBCL Efficacy Set. The EAG's clinical experts considered that the

Kaplan-Meier curves for the naive (unmatched and unadjusted) comparison and the MAIC primary and sensitivity analyses (MAIC Report Figures 3 to 6) are supportive of liso-cel having similar PFS to axi-cel.

4.4.2 Overall survival

CS Table 36 shows the overall survival results for the primary analysis and both sensitivity analyses, compared to a naive comparison before matching and adjustment was applied. In all MAIC analyses the hazard ratio was relatively [redacted] (ranging from [redacted] to [redacted]) and not statistically significant, with relatively [redacted] confidence intervals. The ESS was lowest for the primary analysis and ranged [redacted] to [redacted], compared to a sample size of N=216 for the starting DLBCL Efficacy Set. The EAG's clinical experts considered that the Kaplan-Meier curves for the naive (unmatched and unadjusted) comparison and the MAIC primary and sensitivity analyses (MAIC Report Figures 8 to 11) are supportive of liso-cel having similar overall survival to axi-cel.

4.4.3 Adverse events

Adverse events included in the MAIC were cytokine release syndrome, neurotoxicity, neurologic events, encephalopathy, aphasia, infections, hypogammaglobulinaemia, prolonged neutropenia, prolonged anaemia, prolonged thrombocytopenia, and febrile neutropenia (CS Table 37; MAIC Report section 3.5.2). The EAG's clinical experts agreed that these AESI cover all adverse events known to be relevant to CAR T-cell therapy and/or the immunosuppression and prior therapies involved.

Odds ratios for each category of adverse event were all consistently [redacted] (and mostly [redacted]) and in most cases [redacted] significant (CS Table 37; MAIC Report Figure 12). Statistical significance [redacted] demonstrated for prolonged neutropenia and prolonged thrombocytopenia (where confidence intervals [redacted]), whilst hypogammaglobulinaemia, aphasia, and grade 5 TEAEs each have borderline confidence intervals and p-values indicating [redacted] statistical significance at the conventional threshold (p=0.05). The company did not apply any adjustment to the interpretation of statistical significance to account for multiple outcome testing. However, we note that the [redacted] were achieved for grade <5 TEAEs, CRS, neurotoxicity, neurologic events, encephalopathy, infections,

prolonged anaemia, and febrile neutropenia despite the reduced statistical power after matching and adjustment, as indicated by an ESS of [redacted] for the safety analyses (CS Table 37). The EAG's clinical experts all agreed that the MAIC results demonstrate that liso-cel has a more favourable overall safety profile than axi-cel.

4.5 Conclusions on the clinical effectiveness evidence

The primary evidence for clinical efficacy and safety of liso-cel compared to axi-cel is from an unanchored MAIC. This is appropriate given the structure of the available evidence for comparison (single-arm studies). However, there are several key uncertainties inherent in the MAIC method (section 4.3.7).

Moreover, the progression-free survival results (section 4.4.1) and overall survival results (section 4.4.2) from the MAIC are [redacted] and therefore difficult to interpret in the context of clinical similarity, equivalence, or non-inferiority as is necessary in cost comparison analysis. Safety results are [redacted] liso-cel (section 4.4.3) but subject to uncertainty (section 4.3.7). The EAG are aware that more complex statistical methods might address some limitations of clinical noninferiority interpretation, but these are likely to be computationally demanding, are not widely used in health technology assessments, and might not reduce uncertainty.[16]

The EAG's three clinical experts all agreed, independently, that despite the substantial limitations of the analysis approach noted above, the evidence is sufficient to conclude that liso-cel has similar clinical efficacy, and a more favourable safety profile, than axi-cel.

5 Summary of the EAG's critique of the cost-comparison evidence submitted

5.1 Review of previous cost effectiveness studies

The EAG identified a recent (2025) review of economic evaluations of CAR-T therapies for relapsed or refractory DLBCL by Tran et al.[17] The authors identified four cost utility analyses that compared axi-cel against liso-cel. [18-21] Note that this is the opposite of the comparison specified in the NICE scope, i.e. liso-cel is the 'comparator' here rather than the 'intervention'. As three studies were conducted in USA[18-20] and one in Japan,[21] each analysis was carried out from a different perspective to the analysis included in the CS. The results from these studies are shown in Table 7. In three of the studies there was a significant increase in incremental QALYs for axi-cel compared to liso-cel, and axi-cel is the preferred treatment, while the study by Parker et al. had similar QALYs for both liso-cel and axi-cel, and liso-cel is the preferred treatment. The review notes that the studies used indirect comparison methods, such as matching adjusted indirect comparison, and there was therefore substantial uncertainty in the model results.

Table 7 Economic evaluation studies that compared axi-cel against liso-cel from Tran et al. [17]

Study, year	Interven-tion	Comparator	Incremental		ICER, (US$ / QALY)
			QALYs	Costs	
Oluwole et al,[19]	Axi-cel	Liso-cel	1.82	$14,266	$7,843
Joyner et al, [18]	Axi-cel	Liso-cel	1.807	$16,167	$11,151
Parker et al. [20]	Liso-cel	Axi-cel	0.002	-$74,980	Dominant
Tsutsue et al, [21]	Axi-cel	Liso-cel	2.24	-¥34,122	Dominant
Source: EAG table QALY, quality adjusted life years; ICER incremental cost effectiveness ratio.					

5.2 Decision problem for the cost comparison

5.2.1 Population, intervention and comparator

The population for the appraisal is adults with relapsed or refractory large B-cell lymphoma who are suitable to receive CAR-T cell therapy at third line or later (3L+). This includes the following patients:

- Patients who relapse less than 12 months after first-line therapy but do not receive autologous stem cell transplant (ASCT) due to ineligibility, and then relapse or progress after second-line immunochemotherapy and are suitable for CAR-T therapy at third line.
- Patients who relapse more than 12 months after first-line treatment and are eligible for second-line line ASCT but do not respond to re-induction treatment and remain suitable for CAR-T therapy at third line.
- Patients who relapse following second-line ASCT but are still deemed suitable to receive CAR-T-cell therapy.

The intervention in the economic model is lisocabtagene maraleucel (liso-cel), and the comparator is axicabtagene ciloleucel (axi-cel). These both align with the NICE scope, and the EAG consider the comparator to be acceptable.

5.3 Company's model structure

The company conducted a simple cost comparison analysis in Microsoft Excel comparing the costs associated with liso-cel and axi-cel. Patient outcomes over time were not modelled through a cost-effectiveness model. This is because CAR-T cell therapy is a one-off therapy, and the company assume liso-cel and axi-cel have similar efficacy, with the only long-term cost being for intravenous immunoglobulin replacement therapy (IVIg) for hypogammaglobulinaemia. Therefore the model has no formal time horizon and does not include discounting.

5.3.1 Assumptions

The company make the following assumptions in the cost comparison model (see CS section B.4.2.1):

- Liso-cel and axi-cel have similar efficacy for overall survival and progression free survival
- Subsequent treatments are likely to be similar between patients in both arms across treatment years (see section 2.2.6) and therefore costs of subsequent treatment are not included in the model
- An equal proportion of patients in both arms are infused with CAR-T therapy, informed by the proportion of patients that received a conforming product in the TRANSCEND study ([redacted]).[22]
- An equal proportion of patients in both arms (93.75%) receive bridging therapy prior to CAR-T cell therapy, as informed by feedback from UK CAR-T experts.

5.3.2 EAG conclusion on model structure and assumptions

The cost comparison model does not include survival estimates, adverse events, mortality, utility data, subsequent treatments, or resource use beyond IVIg and intensive care unit (ICU) admissions. The company assume these inputs are equal in both liso-cel and axi-cel arms. As a result, the EAG are unable to test the impact of varying these parameter inputs on the cost comparison results. However, based on clinical evidence (section 4) and the opinion of the EAG's clinical experts, liso-cel and axi-cel are likely to have similar clinical effectiveness and resource use.

5.4 Model parameters

The CAR-T tariff[23] is an all-encompassing cost covering care from the decision for a patient to have CAR-T therapy to 100 days after infusion. The CAR-T tariff for the 2025/26 financial year is £60,462.[24] This cost comprises the following:

- Pre-treatment: leukapheresis and lymphodepleting chemotherapy (LDC)
- Treatment: CAR-T therapy administration costs

- Post-CAR-T therapy infusion: resource use and adverse event management costs up to 100 days after infusion.

The CAR T tariff does not include the following:

- Acquisition costs for CAR-T therapy (liso-cel or axi-cel)
- Bridging therapy costs
- IVIg costs for treating hypogammaglobulinaemia
- ICU costs.

5.4.1 Drug acquisition costs

The company present the drug acquisition costs for liso-cel and axi-cel in CS Table 44. The patient access scheme (PAS) price for liso-cel is [redacted] and the list price for axi-cel is £280,451. Both treatments are administered as a one-off dose intravenously; the costs of administration are included in the CAR-T tariff and are not explicitly modelled in the company's economic model. Patients that receive a non-conforming product in either arm do not incur the CAR-T tariff in the cost comparison model, in line with the approach taken in NICE TA872[1] and reflective of UK clinical practice, given this cost will be absorbed by the company and will not be incurred by the NHS.

5.4.2 Bridging therapies

The company estimated that 93.75% of patients in both arms would receive bridging therapy after leukapheresis, prior to a CAR-T-cell infusion, as informed by feedback from UK CAR-T experts.[25] The distribution of bridging therapies implemented in the cost comparison model, presented in Table 8 below, was assumed to be equal in both arms. The EAG's clinical experts noted that the use of Pola-BR has declined in recent years and the current usage is approximately 5%. The EAG have run a scenario altering the bridging therapy distribution; see section 6.3.

Table 8 Distribution of bridging therapies in the liso-cel and axi-cel arms of the cost comparison model

Bridging therapy	Percentage of patients
R-GemOx	13.00%
Pola-BR	20.77%
GDP	14.59%
R-ICE	8.19%
Radiotherapy	54.70%
Source: Company's cost comparison model and CS section B.4.2.6 R-GemOX, rituximab, gemcitabine and oxaliplatin; Pola-BR, polatuzumab vedotin, bendamustine and rituximab; GDP, gemcitabine, dexamethasone and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin and etoposide.	

5.4.3 Healthcare resource use

5.4.3.1 Treatment for hypogammaglobulinaemia

Immunoglobulin replacement therapy for treating hypogammaglobulinaemia is not included in the CAR-T tariff and therefore is included as a separate cost in the company model. Although in practice approximately 20-25% of patients receive treatment subcutaneously (CS section B.4.2.3), the company assume that all patients receive treatment intravenously (IVIg). Management costs for both Grade 1 and Grade 2 hypogammaglobulinaemia are assumed to be equal at £665, equivalent to the cost of administration of simple parental chemotherapy.[26] IVIg is assumed to be administered every 4 weeks for a duration of 6.5 months in both treatment arms, informed by NICE TA872.[1] In the base case the proportions of patients requiring IVIg are [redacted] and [redacted] (CS Table 45) in the liso-cel and axi-cel arms, respectively (from MAIC Report Table 18). Two of the EAG's three clinical experts agreed that the proportion of patients requiring IVIg would be higher for patients in the axi-cel arm and noted that IVIg usage is increasing; the third expert expected that use of IVIg would be equal in both arms and higher than the figures used by the company. The EAG have therefore explored a scenario with 12.4% and 32% IVIg usage for liso-cel and axi-cel, respectively, double that of the base case values; see section 6.3.

5.4.3.2 Intensive care unit (ICU) usage

ICU admissions and costs are not included in the CAR-T tariff and are modelled separately in the cost comparison model. The company only include the cost of acute ICU stay, and exclude any additional costs associated with long-term rehabilitation. The ICU costs are based on the proportion of patients requiring ICU admission and the duration of the stay. The company assume an average duration of 7.5 days for both treatment arms, informed by NICE TA872.[1] The cost per day in the ICU is £6,605.79, which is a weighted average of Healthcare Resource Group (HRG) codes SA31A-SA31F (malignant lymphoma including Hodgkin's and Non-Hodgkin's, CC Scores 0 to 15+).[26] The proportions of patients requiring ICU stay are [redacted] and [redacted] (CS Table 46) for liso-cel and axi-cel, respectively. These values are informed by French Real World Data using liso-cel at second line.[27] The EAG's clinical experts agreed that axi-cel would have a higher proportion of patients admitted to ICU than liso-cel; however, one expert noted that the proportion for liso-cel is approximately 5% in clinical practice, with another stating that no patients treated with liso-cel have been admitted to ICU in their clinic. Further, one expert estimated that the average stay for ICU patients is approximately 4 days. The EAG have conducted scenarios exploring this variation in ICU duration and proportion (see section 6.3).

5.4.4 EAG conclusion on model parameters

The company provide data on drug acquisition costs, bridging therapies, IVIg use and ICU admissions. The EAG's clinical experts agreed with the company that resource usage, excluding IVIg and ICU, are equal for both liso-cel and axi-cel in clinical practice. Adverse events such as cytokine release syndrome and neurotoxicity were not included in the model, and therefore the EAG were unable to assess the impact of these in the economic model. However, the EAG's clinical experts noted that the toxicity of liso-cel is lower than that of axi-cel in clinical practice, and so in turn the costs associated with treating these adverse events is likely to be lower for liso-cel than for axi-cel.

5.5 EAG model checks

The CS details the company's approach to clinical expert validation of the clinical assumptions in CS section B.4.2.6. The CS does not mention model validation. The EAG checks of the company's cost comparison model included:

- comparing all parameter values against the CS and the cited source documents.
- checking the calculations in the MS Excel spreadsheet.

The EAG note that the cost for the bridging therapy R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) has been incorrectly calculated. The cost for ifosfamide is taken from carboplatin; the cost for carboplatin is taken from etoposide; and the cost for etoposide is taken from dexamethasone.

We were able to reproduce the original model results (base case and scenarios). We confirm that the evidence sources and the values applied in the cost-comparison model are consistent with their sources.

5.5.1 EAG conclusion on model checks

The cost-comparison model is generally well implemented. We found an error in the calculation of some bridging therapy costs, although the cost of bridging therapies is the same for both axi-cel and liso-cel and so has no impact on incremental costs between the treatments.

6 Company and EAG cost comparison results

6.1 Company cost comparison results

The company present a cost comparison comparing lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) for third-line large B-cell lymphoma. The total cost is based on the CAR-T drug acquisition costs, CAR-T tariff cost, ICU cost and IVIg cost and is shown in CS Table 48 (and below in Table 9). The company base case results are shown with the PAS discount price for liso-cel ([redacted]) and the list price for axi-cel. The results suggest that liso-cel is [redacted] relative to axi-cel with an incremental cost of [redacted]. The EAG note that these analyses include the PAS price only for liso-cel, and the list prices for axi-cel and the bridging therapies. We report results using the PAS discount prices for all treatments (where applicable) in a separate confidential addendum to this report.

Table 9 Company base-case cost-comparison results (liso-cel PAS; axi-cel list price)

Treatment	Bridging therapy	CAR T tariff costs	Acquisition cost	ICU cost	IVIg cost	Total
Liso-cel	£5,626	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	£5,626	[redacted]	[redacted]	[redacted]	£2,017	[redacted]
Increment-al	£0	£0	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Table 48 ICU, intensive care unit; IVIg, intravenous immunoglobulin; PAS: patient access scheme;						

The company conducted scenario analyses varying the ICU usage, IVIg usage and proportions with conforming product, with the results shown in CS Table 49.

6.1.1 EAG corrections to the company model

The EAG corrected the errors we found in the costs of bridging therapy (section 5.5). The revised cost of the bridging therapies is £5,708. The corrections change the total cost for liso-cel and axi-cel but not the incremental costs.

6.2 EAG's cost comparison results

With the exception of the correction to the bridging therapy cost reported in section 6.1.1 above, the EAG have not changed any of the assumptions in the economic model. All EAG results therefore relate to the scenario analyses, as reported in section 6.3 below.

6.3 EAG's scenario analyses

The EAG conducted the following scenario analyses using the corrected company base case model:

- Bridging therapies: reduce Pola-BR to 5% (expert opinion), re-weight other therapies.
- Proportion of patients in ICU: 5% for liso-cel (expert opinion)
- Change length of stay in ICU from 7.5-day average to 4-day average (expert opinion)
- Increase IVIg usage to 12.4% for liso-cel and 32% for axi-cel (expert opinion).

The results of the EAG scenarios are shown in Table 10. The incremental costs in the scenarios range from [redacted] to [redacted].

Table 10 EAG scenarios: PAS price for liso-cel and list price for axi-cel and other medications

Base case	Scenarios	Liso-cel cost	Axi-cel cost	Incremental cost
Company corrected base case		[redacted]	[redacted]	[redacted]
Pola-BR 20%	Pola-BR 5%	[redacted]	[redacted]	[redacted]
ICU stay for liso-cel: [redacted]	5%	[redacted]	[redacted]	[redacted]
Length of ICU stay: 7.5 days	4 days	[redacted]	[redacted]	[redacted]
IVIg: [redacted] for liso-cel, [redacted] for axi-cel	12.4% for liso-cel, 32% for axi-cel	[redacted]	[redacted]	[redacted]
Source: EAG table				

Base case	Scenarios	Liso-cel cost	Axi-cel cost	Incremental cost
ICU, intensive care unit; Pola-BR; polatuzumab, bendamustine and rituximab; IVIg, intravenous immunoglobulin.				

6.4 EAG conclusion on the cost comparison

The company provided a cost comparison model that estimated the difference in costs between liso-cel and axi-cel for relapsed or refractory 3+ line large B-cell lymphoma. The company's model assumes similar overall survival and progression-free survival between liso-cel and axi-cel and that subsequent treatments would be similar.

The EAG identified (and corrected) a minor error in the calculation of the bridging therapies (for R-ICE) but this had no effect on the incremental costs of liso-cel vs axi-cel.

The company's results suggest that liso-cel had an incremental cost of [redacted] compared with axi-cel when using the discounted PAS price for liso-cel and list price for axi-cel. The EAG have not changed any of the assumptions in the economics model. We report results for the company's and EAG's analyses using all available NHS price discounts for axi-cel and the bridging therapies in a confidential addendum to this report.

7 Equalities and innovation

The company have not identified any equality issues relating to this indication for liso-cel (CS section B.1.4).

The company do not discuss whether they consider liso-cel to be an innovative therapy. The EAG's clinical experts all agreed that liso-cel would be a welcome addition to the therapies available for this indication, primarily due to having a more favourable safety profile than axi-cel.

8 EAG commentary on the robustness of evidence submitted by the company

The EAG have not identified any critical issues that would preclude a cost comparison analysis. There are several uncertainties in the evidence, including risks of bias in the clinical studies, incomplete matching of the studies in the MAIC due to inherent limitations of the evidence base, lack of a formal statistical hypothesis to confirm similarity of the clinical effectiveness of liso-cel compared to axi-cel, and some differences in the treatments received between patients on liso-cel and axi-cel pathways, e.g. in bridging therapy. Overall, however, the EAG's clinical experts all agreed that these issues would not have sufficient impact to invalidate a cost comparison and that the company have made best use of the available evidence. The experts concluded that liso-cel has similar clinical effectiveness, and a more favourable safety profile, than axi-cel.

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Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic treatments (review of TA987) [ID6619]

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 Tuesday 3 March 2026** 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 Corrections and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.2, Page 11 states: "The decision problem population also differs from the NICE scope by including lymphoma subtypes which are not specified in the NICE scope."	The text should be amended as follows: "**Whilst the population investigated within the clinical evidence base ~~decision problem population also~~** differs from the NICE scope, **~~by~~** including **additional** lymphoma subtypes which are not specified in the NICE scope**, the population specified within the decision problem includes only DLBCL and PMBCL subtypes, to align with the population considered within the axi-cel appraisal, excluding FL3B even though this is included in the marketing authorisation for liso-cel**."	This sentence should be updated to acknowledge the fact that the population specified in the decision problem has been narrowed compared to the clinical effectiveness evidence and marketing authorisation for liso-cel, in order to align with the population considered within the axi-cel appraisal.	Thank you for highlighting this discrepancy. Section 1.2 should cover the decision problem, not the clinical evidence. We have therefore addressed the company's concerns by removing the last two sentences of section 1.2 which refer to the clinical evidence.
Section 2.2.1, Page 14 states: "Manufacturing time for liso-cel (time from leukapheresis to Qualified	The text should be amended as follows: "Manufacturing time for liso-cel (time from leukapheresis to Qualified Person release) is longer than for	The timeline described by the clinical expert is incorrect. The UK manufacturing time from apheresis to QP release has been between 32-36 days for	Not a factual inaccuracy since we have correctly reported the clinical expert's opinion. However, we have also included the company's clarification in

Person release) is longer than for axi-cel. One of the of the EAG's clinical experts said that at their practice this time is currently 25 to 32 days for liso-cel..."	axi-cel. One of the of the EAG's clinical experts said that at their practice this time is currently **32-36** days for liso-cel... "	the 90th percentile since launch in March 2025.	section 2.2.1 as suggested for completeness of interpretation. We have also added FAC to the table of abbreviations.
Section 2.2.1, Page 14 states: "The expert explained that, following Qualified Person release, time to delivery to the patient is 8-10… "	The text should be amended as follows: "The expert explained that, following Qualified Person release, time to delivery to the patient is **5-7** days for liso-cel…."	The timeline described by the clinical expert is incorrect. Sites can choose what date to have the product delivered, which may be longer time from QP release to earliest delivery date. Since launch, all products can be delivered to sites within 5 days, unless it falls over a weekend, therefore extending it to 7 days, however sites can delay delivery if they wish.	Not a factual inaccuracy since we have correctly reported the clinical expert's opinion. However, we have also included the company's clarification in section 2.2.1 as suggested for completeness of interpretation.
Section 2.2.1, Page 14 states: "Patients need to have more lymphocytes available for manufacture of liso-cel"	The text should be amended as follows: **"The manufacture of liso-cel requires apheresis of sufficient number of CD8+ and CD4+ T-cells, which can be challenging for people with a very low lymphocyte count"**	The statement is incorrect. There is no minimum pre-apheresis lymphocyte count requirement for the apheresis of liso-cel. Due to 1:1 ratio of CD8+ and CD4+ T cells in liso-cel leading to complexities in manufacturing, sufficient levels of CD8+ and CD4+ T cells are	Not a factual inaccuracy since we have correctly reported the clinical expert's opinion. However, we have also included the company's clarification in section 2.2.1 for

		required in the starting apheresed material. This can and is achieved at very low lymphocyte counts but requires high apheresis collection efficiency. Therefore, there is a risk of manufacturing failure with a very low lymphocyte count.	completeness of interpretation.
Section 2.2.6, Page 16 states: "CS Figure 3 does not include any subsequent treatments that patients would receive after being given liso-cel or axi-cel at third-line or later, or subsequent treatments for patients who were eligible for but did not receive third-line or later CAR-T therapy."	The text should be amended as follows: "CS Figure 3 does not **explicitly denote specific** ~~**include any**~~ subsequent treatments that patients would receive after being given liso-cel or axi-cel at third-line or later, ~~**or subsequent treatments for patients who were eligible for but did not receive third-line or later CAR-T therapy**~~. **However, multiple treatments included within the figure are recommended for use after two or more subsequent treatments and would therefore be considered relevant**	The figure outlines all the available treatment options at 3L and, as such, the treatment options for patients who do not receive axi-cel or liso-cel at 3L. Epcoritamab (TA954), glofitamab (TA927) and loncastuximab tesirine (TA947) are recommended by NICE for use after two or more systemic treatments (3L+) and the recommendation for pola+BR (TA649) is not limited by treatment line. Thus, these treatment options could be given after liso-cel or axi-cel at 3L.	Not a factual inaccuracy. The EAG are referring to subsequent treatments, not "all the available treatment options at 3L". However, to complete the description of the treatment pathway we have added the company's FAC clarification in section 2.2.6.

	subsequent treatments to axi-cel or liso-cel."		
Section 3.1, Page 18 states: "This is appropriate as it matches the population for which the comparator therapy (axi-cel) was assessed (TA872)[1] and reflects the company's marketing authorisation."	The text should be amended as follows: "This is appropriate as it matches the population for which the comparator therapy (axi-cel) was assessed (TA872)[1] and **is within** the company's marketing authorisation."	The population specified within the decision problem does not fully reflect the marketing authorisation of liso-cel, which also includes patients with FL3B.	Thank you for highlighting this discrepancy. We have amended the text in section 3.1 as suggested.
Section 3.1, Page 18 states: "The decision problem population also differs from the NICE scope by including DLBCL transformed from follicular lymphoma (tFL), DLBCL transformed from indolent non-Hodgkin lymphoma (tiNHL), high-grade lymphoma (HGL), and follicular lymphoma grade 3B (FL3B) which	The text should be amended as follows: "The ~~**decision problem population**~~ **population investigated within the clinical evidence base** also differs from the NICE scope by including DLBCL transformed from follicular lymphoma (tFL), DLBCL transformed from indolent non-Hodgkin lymphoma (tiNHL) **and** high-grade lymphoma (HGL) and follicular lymphoma grade 3B (FL3B) which are not specified in the NICE scope. **However, the population specified in the decision problem does exclude FL3B, despite being**	This sentence should be updated to acknowledge the fact that the population specified in the decision problem has been narrowed compared to the clinical effectiveness evidence and marketing authorisation for liso-cel, in order to align with the population considered within the axi-cel appraisal.	Thank you for highlighting this potential for misinterpretation. We have amended the wording in section 3.1 to clarify the differences between the NICE scope and the decision problem and between the NICE scope and the clinical evidence.

are not specified in the NICE scope."	**included within the clinical evidence base and marketing authorisation for liso-cel**."		
Section 3.1, Page 19, Table 2 caption states: "Types of large B-cell lymphoma (LBCL) included by the company"	This text should be amended as follows: "Types of large B-cell lymphoma (LBCL) included ~~**by**~~ **in** the **TRANSCEND trial** ~~**company**~~"	This heading should be updated to reflect that the subtypes of LBCL outlined in Table 2 are part of the clinical effectiveness evidence, rather than the decision problem population.	Not a factual inaccuracy. Table 2 does not refer to the decision problem and TRANSCEND is the source of evidence provided by the company. No change made.
Section 3.1, Page 19, Table 2, row 3, column 2 states: "Not described in the CS…"	This text should be amended as follows: "~~**Not described in the CS**~~. **Although this subtype was included in the TRANSCEND study, the Company have excluded this subtype as part of the population considered within the decision problem of this appraisal. As such, the company is not making a case for reimbursement of this subtype**…"	This text should be updated to reflect that some of the subtypes of LBCL outlined in Table 2, which are included within the population in the TRANSCEND trial, are not considered within the decision problem of this appraisal.	Not factual inaccuracies. Table 2 lists and defines the different subtypes of LBCL that are included in the clinical evidence in the CS. All of these (HGL, tFL, tiNHL, PMBCL, FL3B) are included in the clinical evidence reported for the TRANSCEND study in CS section B.3.6.1. All of them except FL3B, because it is excluded from the decision problem, are also included in the MAIC analysis (CS Table 29) used for
Section 3.1, Page 19, Table 2, row 4, column 2 states:	This text should be amended as follows: "~~**Not described in the CS**~~. **Although this subtype was**	This text should be updated to reflect that some of the subtypes of LBCL outlined in Table 2, which are included	

"Not described in the CS…"	**included in the TRANSCEND study, the Company have excluded this subtype as part of the population considered in this appraisal. As such, the Company is not making a case for reimbursement of this subtype**…"	within the population in the TRANSCEND trial, are not considered within the decision problem of this appraisal.	comparative evidence versus axi-cel. No changes made, except to amend Table 2 row 6 to clarify that FL3B is excluded from all MAIC analyses. As we have reported, the EAG's clinical experts unanimously agreed that pragmatic inclusion of these subtypes is reasonable and is consistent with the approach in TA872.
Section 3.1, Page 19, Table 2, row 5, column 2 states: "Not described in the CS…"	This text should be amended as follows: "~~**Not described in the CS**~~. **Although this subtype was included in the TRANSCEND study, the Company have excluded this subtype as part of the population considered within the decision problem of this appraisal. As such, the Company is not making a case for reimbursement of this subtype**…"	This text should be updated to reflect that some of the subtypes of LBCL outlined in Table 2, which are included within the population in the TRANSCEND trial, are not considered within the decision problem of this appraisal.	
Section 3.1, Page 20, Table 2, row 6, column 2 states: "Not described in the CS…"	This text should be amended as follows: "~~**Not described in the CS**~~. **Although this subtype was included in the TRANSCEND study, the Company have excluded this subtype as part of the population considered within**	This text should be updated to reflect that some of the subtypes of LBCL outlined in Table 2, which are included within the population in the TRANSCEND trial, are not considered within the decision problem of this appraisal.	

	the decision problem of this appraisal. As such, the Company is not making a case for reimbursement of this subtype…"		
Section 3.1, Page 25, Table 3, row 5, column 5 states: "NICE's criteria for economic analysis have been followed, except that the company do not explicitly discuss the time horizon for the assessment, although this does not invalidate the cost comparison (see section 5.3 below)."	The text should be amended as follows: "NICE's criteria for economic analysis have been followed~~, except that the company do not explicitly discuss the time horizon for the assessment, although this does not invalidate the cost comparison (see section 5.3 below)~~."	As stated in Section 5.3 of the EAG report and Section B.4.2.1 of the CS, given the one-off nature of CAR T-cell therapies, and assumed similar efficacy between liso-cel and axi-cel, no long-term costs beyond IVIg treatment, or long-term efficacy outcomes were modelled and, therefore, no formal time horizon was considered.	Thank you for highlighting this inaccuracy. We have corrected the text in Table 3.
Section 3.2, Page 27 states: "The decision problem is narrower than the NICE scope which is appropriate to align with the company's marketing authorisation and the specific type of therapy. The decision problem	The text should be amended as follows: "The decision problem is narrower than the NICE scope **to align with the population considered within the axi-cel appraisal**, ~~which is appropriate to align with~~ **and is within** the company's marketing authorisation **for liso-cel** ~~and the specific type of therapy~~. The	The population considered within the decision problem has not been narrowed to align with the marketing authorisation, given the marketing authorisation also includes patients with FL3B. Instead, the population has been narrowed in order to align with the population considered within	Thank you for highlighting this inconsistency. We have amended the text in section 3.2 to correct this.

population includes lymphoma subtypes that are not specified in the NICE scope but the EAG's clinical experts considered this appropriate for the present cost comparison analysis."	~~**decision problem population**~~ **Company clinical evidence** includes lymphoma subtypes that are not specified in the NICE scope **and were excluded from the decision problem population,** but the EAG's clinical experts considered this appropriate for the present cost comparison analysis."	the axi-cel appraisal (i.e., excluding FL3B).	
Section 4.2.2.2, Page 30 states: "…since a single infusion of DL1 in the study is a lower dose than would be used in practice, whilst the double infusion of DL1 would give the same total dose as in clinical practice."	The text should be amended as follows: "…since a single infusion of DL1 in the study is a lower **target** dose than would be used in practice **(50 x 10^6 CAR-positive viable T-cells)**, whilst the double infusion of DL1 would give the same total **target** dose as in clinical practice **(100 x 10^6 CAR-positive viable T-cells); however, both DL1S and DL1D would achieve a total dose within the target range specified in the SmPC (44-120 x 10^6 CAR-positive viable T-cells)**."	This sentence should be updated to clarify that both the DL1S and DL1D dosing schedules fall within the target dose range outlined within the SmPC.	Not a factual inaccuracy. However, we agree that additional clarification would be helpful as suggested by the company and we have amended the text in section 4.2.2.2 accordingly.
Section 4.2.2.2, Page 31 states:	The text should be amended as follows:	This sentence should be updated to clarify that DL1S and DL1D both fall within the	Not a factual inaccuracy. The text referred to here is a summary sentence. The

"In summary, there are some deviations of the dosing regimens in TRANSCEND from both the marketing authorisation and anticipated clinical practice but the EAG's clinical experts did not expect these would compromise the generalisability of the study results."	"In summary, there are some deviations of the dosing regimens in TRANSCEND from both the marketing authorisation and anticipated clinical practice, **albeit still falling within the target dose range specified in the SmPC. In addition, the majority of patients in the TRANSCEND trial received DL2 (n=178/229; 78%) which is aligned with the dose patients are anticipated to receive in UK clinical practice.** ~~**but**~~ The EAG's clinical experts did not expect these would compromise the generalisability of the study results."	target dose range outlined within the SmPC, and that the majority of patients in the trial did receive the DL2 dosing regimen, in line with UK clinical practice.	more detailed information suggested by the company is already present in the main paragraph of section 4.2.2.2. No change made.
Section 4.2.2.3, Page 31 states: "The company provided three analysis sets for TRANSCEND (CS Table 9) that are relevant to the population being appraised (summarised in Table 5 below)."	The text should be amended as follows: "The company provided three analysis sets for TRANSCEND (CS Table 9) **and one analysis set for GC-LTFU-001** that are relevant to the population being appraised (summarised in Table 5 below)."	This statement should be updated to reflect that three of the analysis sets in Table 5 are from TRANSCEND, and one is from GC-LTFU-001.	Thank you for suggesting this clarification. We note that two analysis sets in CS Table 9 include data from GC-LTFU-001. We have amended the text in section 4.2.2.3 to ensure that the citation of information in CS Table 9 and EAG Report Table 5 is accurate.

Section 4.2.2, Page 29, Table 4, row 5, column 2 states: "Efficacy Set N= 216; Treated Set (safety) N=229…"	This text should be amended as follows: "**DLBCL Cohort** Efficacy Set N=216; **DLBCL Cohort** Treated Set (safety) N=229…" In addition, the following text should be included above the table: "**The analysis sets are based on the TRANSCEND "DLBCL Cohort" which consists of participants with the lymphoma subtypes DLBCL, HGL, PMBCL and FL3B (CS Table 10) (for a description of the lymphoma subtypes see Table 2 above)**."	As this is the first mention of the relevant analysis sets, the wording should be updated to clarify that the Efficacy and Treated sets are based on the DLBCL Cohort of TRANSCEND.	Not a factual inaccuracy but thank you for this suggestion. We have clarified in Table 4 that the analysis sets are based on the DLBCL cohort. Additionally, we have updated the heading of the first column of Table 5 to reflect this, and we have added cross-references in Table 4 to section 4.2.2.3 where the analysis sets are further explained.
Section 4.2.2.3, Page 31, Table 5 caption states: "TRANSCEND analysis sets used in the CS"	The text should be amended as follows: "TRANSCEND **and GC-LTFU-001** analysis sets used in the CS"	This statement should be updated to reflect that three of the analysis sets in Table 5 are from TRANSCEND, and one is from GC-LTFU-001.	Thank you for highlighting this inconsistency. We note that two of the analysis sets in CS Table 9 and EAG Table 5 include data from GC-LTFU-001. We have amended the caption of Table 5 accordingly.
Section 4.2.3, Page 32 states:	The text should be amended as follows:	The sentence is misleading and should be corrected to clarify that quality assessments were	Not a factual inaccuracy. Quality assessment results are reported in CS Table 15

"…Downs and Black checklist,[14] (CS Appendix 12) but only provided a risk of bias interpretation for TRANSCEND which they assessed to be at low risk of bias (CS section B.3.5)"	"…Downs and Black checklist,[14] (CS Appendix 12) ~~**but only provided a risk of bias interpretation for**~~ **and assessed the** TRANSCEND **trial** ~~**which they assessed**~~ to be at low risk of bias (CS section B.3.5). **Risk of bias assessments for the other published studies presented within the submission were presented within the clinical SLR report.**"	conducted for all studies for which published data are available.	for TRANSCEND, CS Appendix Table 11 for TRANSCEND and ZUMA-1, and in SLR Report Table 10 for TRANSCEND and OUTREACH. In all cases the Downs and Black questions have been left as "yes" or "no" answers, with no explanation of whether these translate to low, high, or unclear risk of bias judgements. For TRANSCEND an overall "low" risk of bias is mentioned by the company but it is unclear how this was reached as it does not explicitly link to the question answers. No quality assessment has been provided for GC-LTFU-001 or TRANSCENDWORLD despite the company having data for these unpublished studies. No change made.
Section 4.2.5, Page 33 states:	The text should be amended as follows:	This statement should be updated in order to accurately reflect the statistical analysis	Thank you for highlighting this inaccuracy. We have amended the text in section

"…the statistical power calculation in TRANSCEND applies to the achievement of ORR rather than the survival outcomes."	"…the statistical power calculation in TRANSCEND applies to the achievement of ORR **and CR** rather than the survival outcomes."	methods of the TRANSCEND trial.	4.2.5 as requested. We also noticed an incorrect definition of ORR in the table of abbreviations and have corrected this.
Section 4.2.5.2, Page 34 states: "There are slight differences in the confidence interval as reported in CS Table 36 and in CS section B.3.11 but these do not affect the clinical interpretation (section 4.2.5.3 below)."	The text should be amended as follows: "~~**There are slight differences in the**~~ **The** confidence interval ~~**as**~~ reported in CS Table 36 **is incorrect**, ~~**and**~~ **with the correct value reported** in CS section B.3.11 but ~~**these**~~ **this discrepancy does** ~~**do**~~ not affect the clinical interpretation (section 4.2.5.3 below)."	The Company have provided clarity here on which values are correct.	Thank you for clarifying which value is correct. We have removed unnecessary text relating to this in section 4.2.5.2.
Section 4.2.6, Page 35 states: "The company do not provide a rationale in the CS for the two safety assessment periods; the study statistical analysis plan appears to indicate that after 90 days an adverse event is no	The text should be amended as follows: "**The treatment-emergent period for TEAE evaluation started any time from initiation of liso-cel administration and up to 90 days following the final cycle of liso-cel, as outlined in the TRANSCEND 2021 Addendum CSR provided within the**	The Company have provided clarity here on why TEAEs and post-TEAEs were reported.	Thank you for providing this clarity. We have amended the text in section 4.2.6 as suggested with some edits for brevity and to avoid repetition: "Post-TEAEs were reported to assess long-term toxicity, and viral vector safety for up to 15 years post-last dose of liso-

longer considered related to liso-cel treatment, but it is not clear."	**reference pack accompanying the submission. Post-TEAEs were reported to assess long-term toxicity, and viral vector safety for up to 15 years post-last dose of liso-cel, in accordance with health authority guidance on viral vector-based gene therapy products, as outlined in the TRANSCEND 2024 CSR provided within the reference pack accompanying the submission.** ~~**The company do not provide a rationale in the CS for the two safety assessment periods; the study statistical analysis plan appears to indicate that after 90 days an adverse event is no longer considered related to liso-cel treatment, but it is not clear**~~."		cel, in accordance with health authority guidance on viral vector-based gene therapy products (TRANSCEND 2024 CSR page 12)."
Section 4.3.1, Page 37 states: "The company acknowledge that it is virtually impossible to adjust for all possible factors that may differ between studies…"	The text should be amended as follows: "The company acknowledge that it is virtually impossible to adjust for all possible factors that may differ between studies**; however, a rigorous, multi-faceted process was used to identify and rank**	This sentence is misleading and should be updated in order to acknowledge the steps taken by the Company to minimise this risk of bias.	Not a factual inaccuracy. The EAG have accurately cited the company's acknowledgement of the evidence limitations and the detailed steps taken by the company in their analyses. The additional text proposed by the company

	factors, and the primary and sensitivity analyses were consistent, supporting the robustness of the conclusions…"		does not alter the MAIC conclusions. No change made.
Section 4.3.3.2.1, Page 39 states: "For safety outcomes the same factors were removed from TRANSCEND except that disease histology is not listed, without an explanation (MAIC Report Table 20)."	The text should be amended as follows: "For safety outcomes, **the same process for factor identification was used ~~the same factors were removed from TRANSCEND except that disease histology is not listed, without an explanation (MAIC Report Table 20)~~**."	The text here should be updated to accurately reflect the clarity provided on the approach to identifying the relevant clinical factors for matching in the safety analyses, provided below. Clinical factors considered for adjustment were identified and selected based on a targeted literature review, clinical expert opinions, and data availability (MAIC Report Section 8.2). The final rank-order was based on the reporting frequency in the literature base together with key factors suggested by four clinical experts. Disease history was not identified in the targeted literature review nor suggested by the clinical experts consulted. Thus, it was not considered for the safety MAIC.	Not a factual inaccuracy. However, we have amended the text in section 4.3.3.2.1 to clarify the rationale for exclusion of disease histology from consideration.

Section 4.3.3.2.1, Page 40 states: "Sensitivity analyses were not conducted for safety outcomes, but the CS and MAIC Report do not explain why not."	The text should be amended as follows "Sensitivity analyses were not **presented** ~~**conducted**~~ for safety outcomes **within the submission, to ensure conciseness within the CS** ~~**the CS and MAIC Report do not explain why not**~~."	The wording should be updated to reflect the clarity provided by the Company below on the sensitivity analyses conducted for safety outcomes. Sensitivity analyses were conducted by varying the number of clinical factors adjusted for, with the evidence consistently suggesting that liso-cel was associated with statistically significantly improved safety profile compared with axi-cel across all analyses.	Not a factual inaccuracy. No explanation is given in the CS or MAIC Report as to why the sensitivity analysis results for safety outcomes are missing. No change made.
Section 4.3.3.2.2, Page 40 states: "…whilst footnote 'c' in MAIC Report Table 19 indicates two factors were not available in the ZUMA-1 efficacy set."	The text should be amended as follows: "…whilst footnote 'c' in MAIC Report Table 19 indicates two factors **(Cell of origin and Double/Triple Hit or Double Expressor)** were not available in the ZUMA-1 efficacy set **and were available for the safety set only**."	This sentence should be updated to accurately reflect the data available.	Not a factual inaccuracy. However, since the MAIC Report will not be available in the NICE committee papers we have amended the text as suggested to enable interpretation.
Section 4.3.3.2.2, Page 41 states:	The text should be amended as follows:	This text should be updated to accurately reflect the clarity	Not a factual inaccuracy. However, we have

"For safety analysis, MAIC Report section 8.3.1 mentions 12 clinical factors were available for comparison (section **Error! Reference source not found.** above), but MAIC Report section 4.3.1.2 states nine clinical factors were included. The reason for this discrepancy is unclear. Four of the nine factors were included in matching as described above (section **Error! Reference source not found.**), and the remaining five were adjusted in the MAIC (MAIC Report section 4.3.1.2), but it is unclear which three factors listed in MAIC Report Table 20 were omitted from adjustment or why."	"For safety analysis, MAIC Report section 8.3.1 mentions 12 clinical factors were available for comparison (section 4.3.3.1 above). **Bone marrow involvement was excluded from the safety MAIC. Of the remaining eleven factors, two were not included within the base case analysis (age and prior auto-HSCT), four were matched as described above (section 4.3.3.2.1), and the remaining five were adjusted in the base case analysis (MAIC Report section 4.3.1.2). A sensitivity analysis was conducted including all eleven factors**. ~~**but MAIC Report section 4.3.1.2 states nine clinical factors were included. The reason for this discrepancy is unclear. Four of the nine factors were included in matching as described above (section 4.3.3.2.1), and the remaining five were adjusted in the MAIC (MAIC Report section 4.3.1.2), but it is unclear which three factors listed in MAIC Report Table 20 were omitted from adjustment or why**~~."	provided by the Company on the clinical factors matched and adjusted for in the safety analyses, provided below. Bone marrow involvement was excluded from the safety MAIC since assessment by bone marrow biopsy at baseline was not required in TRANSCEND and, as such, including bone marrow involvement in the MAIC reduced the ESS to <20 and resulted in extreme patient weights, rendering analyses unreliable. The base case was selected based on achieving a balance between the performance and suitability criteria of each MAIC model (such as ESS and SMDs) and the number of factors included.	reproduced the company's statement in section 4.3.3.2.2 to resolve the uncertainty in the company's methods described in the EAG Report.

Section 4.3.3.2.3, Page 41 states: "The primary analysis achieved relatively poor matching compared to the sensitivity analyses, having the highest proportions of clinical factors with SMD ≥0.2 (around [redacted]%) after matching (CS section B.3.9.5 and MAIC Report section 5.1.1.1), and the lowest ESS values (PFS [redacted], OS [redacted]), together with some high patient weights (CS Tables 35 and 36)."	The text should be amended as follows: "**Given the limitations of the evidence base, in that bridging therapies were not permitted in the ZUMA-1 trial, requiring many patients from the TRANSCEND trial to be excluded,** the primary analysis achieved relatively poor matching compared to the sensitivity analyses, having the highest proportions of clinical factors with SMD ≥0.2 (around [redacted]%) after matching (CS section B.3.9.5 and MAIC Report section 5.1.1.1), and the lowest ESS values (PFS [redacted], OS [redacted]), together with some high patient weights (CS Tables 35 and 36)."	This sentence is misleading and should be updated to acknowledge the limitations of the evidence base.	Not a factual inaccuracy. The EAG are merely stating which analyses had good/poor matching and we do not agree that our statement is misleading. The limitations of the evidence are clearly acknowledged in the EAG Report. No change made.
Section 4.3.3.2.3, Page 41 states: "The matching between TRANSCEND and ZUMA-1 was also suboptimal for the safety outcomes, particularly for patient age (SMD 0.554) MAIC Report Table 29)."	The text should be amended as follows: "The matching between TRANSCEND and ZUMA-1 **was generally good for safety outcomes, with the majority of characteristics with SMD<0.2; however,** was ~~**also**~~ suboptimal ~~**for the safety outcomes, particularly**~~	This sentence is misleading given the majority of characteristics had a SMD<0.2, which indicates that the matched population was well adjusted for potential treatment effect modifiers or prognostic factors.	Thank you for highlighting the potential for the text to be misleading. We have added further detail for clarity in section 4.3.3.2.3, referencing also the patient weights and ESS for consistency with how the clinical efficacy results are reported. We have also

	for patient age (SMD 0.554~~);~~ MAIC Report Table 29)."		corrected an error in the citation of CS Tables 35 and 36).
Section 4.3.4, Page 41 states: "…low risk of bias in TRANSCEND (CS section B.3.5), but have not provided an opinion on the risk of bias in ZUMA-1."	The text should be amended as follows: "…low risk of bias in TRANSCEND (CS section B.3.5), ~~**but have not provided an opinion on**~~ **and ZUMA-1, with the risk of bias in ZUMA-1 presented in the clinical SLR (Appendix E, Table 4)**."	This sentence requires correction, as the RoB assessment for ZUMA-1 was provided within the clinical SLR, with a score of 20 (low risk of bias).	Not a factual inaccuracy. The company only report Yes/No responses to items, with no rationale for the responses, and a score of 20 for overall quality assessment in Table 4, Appendix E, of the clinical SLR 2021 report (separate document for appendices). The company have not provided an opinion on risk of bias in ZUMA-1. No change made.
Section 4.3.4, Page 41 states: "…We consider both the TRANSCEND and ZUMA-1 studies to have an inherently high risk of bias due to being uncontrolled and open-label studies."	The text should be amended as follows: ""…**Whilst** we consider both the TRANSCEND and ZUMA-1 studies to have an inherently high risk of bias**,** due to being uncontrolled and open-label studies**, the internal validity of the studies is supported by robust conduct and**	The current statement is misleading and should be updated to acknowledge the internal validity of both studies.	Not a factual inaccuracy. The EAG's statement explicitly reports our judgement of the risk of bias – i.e. the internal validity – of both studies. No change made.

	comprehensive outcome reporting."		
Section 4.3.6, Page 43 states: "…but we note that matching and adjustment was not entirely successful at balancing the study populations in the primary analysis…"	The text should be amended as follows: "…but we note that matching and adjustment was not entirely successful at balancing the study populations in the primary analysis, **given the inherent limitations of the evidence base for this submission, in that the majority of patients in TRANSCEND received bridging therapies ([redacted]%), whilst bridging therapy was not permitted in ZUMA-1**…"	This sentence is misleading and should be updated to acknowledge the limitations of the evidence base.	Not a factual inaccuracy. The limitations of the evidence base are clearly acknowledged in the EAG Report. The company's suggested amendment could be misunderstood to mean that the only difference between the trials was in bridging therapy. No change made.
Section 4.3.7, Page 43 states: "The analysis of safety outcomes was less detailed than that of the clinical efficacy outcomes, with an abbreviated ranking process (section 4.3.3.1), no sensitivity analyses conducted (section 4.3.3.2.1), and there are	The text should be amended as follows: "The analysis of safety outcomes was less detailed than that of the clinical efficacy outcomes, with an abbreviated ranking process (section 4.3.3.1). ~~**no**~~ T**hree** factors **were** ~~**/**~~excluded from the **base case** safety analysis (section 4.3.3.2.2), but sensitivity analyses **were** conducted demonstrating **that liso-cel was associated with**	The Company have provided clarity on the MAIC safety analyses.	Not a factual inaccuracy. This is a summary bullet that cannot contain the level of detail suggested by the company, which we have already included in section 4.3.3.2.2 in response to similar comments above. However, we have amended the bullet so that it aligns with the change made in section 4.3.3.2.2.

ambiguities in the factors included/excluded from the safety analyses (section 4.3.3.2.2)."	**statistically significantly improved safety profile compared with axi-cel, although not presented within the CS for conciseness** (section 4.3.3.2.1). ~~**and there are ambiguities in the factors were included/excluded from the base case safety analysis analyses (section 4.3.3.2.2).**~~**"**		The company's description of the sensitivity analysis appears inconsistent. The company's comments above relating to section 4.3.3.2.2 state that there was one sensitivity analysis but here several are mentioned. No results of any safety sensitivity analyses are provided and therefore the EAG cannot draw any inferences relating to these. "Conciseness" is not an appropriate reason for excluding key results and is not mentioned as the reason in the CS or MAIC Report.
Section 5.1, Page 47 states: "The authors identified four cost utility analyses that compared axi-cel against liso-cel.[18-21] Three studies were conducted in USA18-[20] and one in Japan.[21]"	This text should be amended as follows: "The authors identified four cost utility analyses that compared axi-cel against liso-cel.[18-21] **As** three studies were conducted in USA[18-20] and one in Japan,[21] **each analysis was carried out from a different**	This section should be amended to reflect the limitations of the economic evaluations used to compare axi-cel and liso-cel.	Thank you for highlighting the missing information on study limitations. We have amended the text in section 5.1 as suggested.

	perspective to the analysis included in the CS."		
Section 5.1, Page 47 states: "In three of the studies there was a significant increase in QALYs for axi-cel compared to liso-cel, and axi-cel is the preferred treatment, while the study by Parker et al. had similar QALYs for both liso-cel and axi-cel, and liso-cel is the preferred treatment. The review notes that the studies used indirect comparison methods, such as matching adjusted indirect comparison, and there was therefore substantial uncertainty in the model results."	This text should be amended as follows: "In three of the studies there was a significant increase in **incremental** QALYs for axi-cel compared to liso-cel, and axi-cel is the preferred treatment, while the study by Parker et al. had similar QALYs for both liso-cel and axi-cel, and liso-cel is the preferred treatment. **However, both the Oluwole et al. and Tsutsue et al. studies select long-term OS and PFS extrapolations based on statistical fit alone, without any consideration of their clinical plausibility. As such, these long-term extrapolations are not aligned with NICE guidelines, as per TSD14. Since the Joyner et al. study was based on the Oluwole et al. study, the same limitation applies. In addition, whilst these studies rely on ITCs to inform the comparative efficacy, there is limited detail available to assess the**	This section should be amended to reflect the limitations of the economic evaluations used to compare axi-cel and liso-cel.	We have amended the text to *incremental QALYs* in section 5.1. However, the extra detail in the proposed amendment does not represent a factual accuracy. We appreciate the company's further information, but we have not completed a full critique of these studies and so are not able to comment on their limitations.

	robustness of the ITC methods. This is highlighted by the EAG who note that there was substantial uncertainty within the model results ~~The review notes that the studies used indirect comparison methods, such as matching adjusted indirect comparison, and there was therefore substantial uncertainty in the model results~~. **In addition, the drug acquisition costs presented for liso-cel and axi-cel are not reflective of UK clinical practice. Finally, Oluwole et al. and Tsutsue et al. assume an equal rate of IVIg use and ICU admissions for liso-cel and axi-cel, which is not clinically plausible nor reflective of UK clinical practice.**"		
Section 5.3.1, Page 48 states: "An equal proportion of patients in both arms (93.75%) receive bridging	The text should be amended as follows: "An equal proportion of patients in both arms (93.75%) receive bridging therapy prior to CAR-T cell therapy,	Additional context should be provided as to the source of this estimate.	Not a factual inaccuracy. However, we have added the information regarding the source of the bridging therapy proportion in

therapy prior to CAR-T cell therapy."	**as informed by feedback from UK CAR-T experts**."		section 5.3.1 for additional clarity.
Section 5.4.1, Page 50 states: "Patients that receive a non-conforming product in either arm do not incur the CAR-T tariff in the cost comparison model and this is in line with the approach taken in NICE TA872."	The text should be amended as follows: "Patients that receive a non-conforming product in either arm do not incur the CAR-T tariff in the cost comparison model**, ~~and this is~~** in line with the approach taken in NICE TA872 **and reflective of UK clinical practice, given this cost will be absorbed by BMS and will not be incurred by the NHS**."	Additional context should be provided to make it clear that this assumption is reflective of UK clinical practice.	Not a factual inaccuracy. However, we have added the information regarding the cost of non-conforming product in section 5.4.1 for additional clarity.
Section 5.4.2, Page 50 states: "The company estimated that 93.75% of patients in both arms would receive bridging therapy after leukapheresis, prior to a CAR-T-cell infusion."	The text should be amended as follows: "The company estimated that 93.75% of patients in both arms would receive bridging therapy after leukapheresis, prior to a CAR-T-cell infusion, **as informed by feedback from UK CAR-T experts**."	Additional context should be provided as to the source of this estimate.	Not a factual inaccuracy. However, we have added the information regarding the source of bridging therapy proportion in section 5.4.2 for additional clarity.
Section 5.4.3.1, Page 51 states: "In the base case the proportions of patients requiring IVIg are [redacted]%	The text should be amended as follows: "In the base case the proportions of patients requiring IVIg are [redacted]% and [redacted]% (CS Table 45) in the liso-cel	In response to Clarification Question B1, the Company provided the source of these data within the MAIC report: Table 18, page 67; row:	Thank you for clarifying this. We have amended the text in section 5.4.3.1 accordingly.

and [redacted]% (CS Table 45) in the liso-cel and axi-cel arms, respectively. The CS mentions that these values were informed by the MAIC, but it is unclear how the information in CS Table 45 relates to the MAIC, and therefore the source of these estimates is unclear."	and axi-cel arms, respectively, **as informed by the MAIC**. ~~**The CS mentions that these values were informed by the MAIC, but it is unclear how the information in CS Table 45 relates to the MAIC, and therefore the source of these estimates is unclear."**~~	"Hypogammaglobulinemia[a], Grouped Term"; columns: "Liso cel (Study 017001) DLBCL Treated Set Dose Levels DL1S + DL2S + DL1D; MAIC, %" and "Axi-cel (ZUMA-1) Phase 1+2 Safety Analysis Set; Reported Rates, %". This sentence should be amended to reflect this clarification.	
Section 8, Page 58 states: "…incomplete matching of the studies in the MAIC…"	The text should be amended as follows: "…incomplete matching of the studies in the MAIC, **due to the inherent limitations of the evidence base for this submission, in that the majority of patients in TRANSCEND received bridging therapies ([redacted]%), whilst bridging therapy was not permitted in ZUMA-1** …"	This sentence is misleading and should acknowledge the limitations of the evidence base.	Not a factual inaccuracy. However, we have clarified in section 8 that the incomplete matching in the MAIC is due to inherent limitations of the evidence base.

Issue 2 Data and typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1, Page 21, Table 3, row 1, column 5 states: "…includes lymphoma subtypes scope (tFL, tiNHL, FL3B) not specified in the NICE and the company have grouped together patients with DLBCL and PMBCL in their analyses."	The text should be amended as follows: "…includes lymphoma subtypes scope (tFL, tiNHL, FL3B) not specified in the NICE **scope** and the company have grouped together patients with DLBCL and PMBCL in their analyses."	This is a typographical error.	Thank you for highlighting this typographical error. This has been corrected.
Section 4.2.1, Page 28 states: "…OUTREACH[11] (NCT03744676))…"	The text should be amended as follows: "…OUTREACH[11] (NCT03744676**)**…"	This is a typographical error.	Thank you for highlighting this typographical error. This has been corrected.
Section 4.3.3.2.1, Page 39 states: "…disease histology is not listed, without an explanation (MAIC Report Table 20)."	The text should be amended as follows: "…disease histology is not listed, without an explanation (MAIC Report Table **11**)."	This is a typographical error.	No longer relevant as the text in question has been removed in response to a previous company comment concerning section 4.3.3.2.1.

Section 4.3.3.2.2, Page 40 states: "Five of these factors were adjusted in the primary analysis…"	The text should be amended as follows: "**Six** of these factors were adjusted in the primary analysis…"	Across the primary MAIC analyses of PFS and OS, a total of six clinical factors were adjusted for. Of these, four were common to both PFS and OS and one each were additionally adjusted for PFS and OS, respectively. The text should be amended to ensure that it is clear that a total of six specific factors were adjusted for within the analysis.	Thank you for highlighting this typographical error. This has been corrected.
Section 5.4.3.1, Page 51 states: "Management costs for both Grade 1 and Grade 2 hypogammaglobulinaemia are assumed to be equal at £655, equivalent to the cost of administration of simple parental chemotherapy."	This should be amended to: "Management costs for both Grade 1 and Grade 2 hypogammaglobulinaemia are assumed to be equal at **£665**, equivalent to the cost of administration of simple parental chemotherapy."	This is a typographical error.	Thank you for highlighting this error; we have amended the value in section 5.4.3.1.
Section 5.5, Page 52 states: "The EAG checks of the company's cost	This should be amended to **include bullet points**.	The two sentences following "included:" are missing bullet points.	Thank you for highlighting this formatting issue, we have inserted the missing bullet points in section 5.5.

comparison model included: comparing all parameter values against the CS and the cited source documents; checking the calculations in the MS Excel spreadsheet…"			

Issue 3 Confidentiality marking errors

Location of incorrect marking	Description of incorrect marking	Amended marking	
Section 4.4.3, Page 45	Details on statistical significance of the results from the MAIC analyses are considered confidential as they are based on unpublished data from the TRANSCEND trial.	The following CiC should be applied: "However, we note that the [redacted] were achieved for grade <5 TEAEs…"	Thank you for highlighting the missing confidentiality marking. This has been added.