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)
Authors	Geoff Frampton, Principal Research Fellow, SHTAC Lois Woods, Senior Research Assistant, SHTAC Asyl Hawa, Research Fellow, SHTAC Keith Cooper, Principal Research Fellow, SHTAC David Scott, Professor, SHTAC
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
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Dr Harriet Walter, Associate Professor of Medical Oncology, University of Leicester and University Hospitals Leicester

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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

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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

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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

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

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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

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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.

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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.

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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

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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

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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).

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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.

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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

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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.

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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

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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.

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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.

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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

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	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

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	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.

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	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,

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	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).

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	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.

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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.

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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

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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)

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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

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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).

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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

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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

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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.

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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).

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[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.

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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

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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

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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

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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,

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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).

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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]

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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:

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- 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

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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,

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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.

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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.					

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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.

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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

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- 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.

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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.

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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.

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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.

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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.

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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				

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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.

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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.

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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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