External Assessment Group report: lisocabtagene-maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Table of Contents

Table of Tables

Table of Issues

Table of Figures

Executive Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (See section 1).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID3887	Summary of issue	Report sections
(1)	Generalisability concerns over the representativeness of TRANSFORM trial for NHS care.	2.6
(2)	Whether to use event-free survival (EFS) or progression free survival on subsequent therapy (PFS2) for economic modelling structure	3.2.2, 3.2.6
(3)	Choice of extrapolation for overall survival (OS)	3.2.6.3
(4)	Choice of extrapolation for time to next treatment (TTNT)	3.2.6.4
(5)	Utility value for "healthy" health state for first 5 years of model	3.2.7
(6)	Bridging therapy distribution	3.2.8.1.2
(7)	Subsequent therapy distribution	3.2.8.3
(8)	Adverse event costs	3.2.8.5

The key differences in QALY estimates between the company's preferred assumptions and the EAG's preferred assumptions are the modelling of OS and EFS/PFS2. The key differences in cost estimates are the distribution of subsequent therapies and adverse events modelled.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival and event-free/progression-free survival.

Overall, the technology is modelled to affect costs by:

- The cost of 2L and subsequent treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- The modelling of overall survival
- The modelling of adverse event costs
- The modelling of subsequent therapies received

1.3 *The decision problem: summary of the EAG's key issues*

The EAG had no key issues relating to the decision problem

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1: Generalisability of the TRANSFORM trial to NHS practice

Report section	2.6
Description of issue and why the EAG has identified it as important	People in TRANSFORM received different previous and subsequent therapies compared to NHS care and they received CAR T treatment more rapidly at 2L and 3L meaning very little dropout between liso-cel leukapheresis and infusion.
What alternative approach has the EAG suggested?	The EAG is unable to fully account for these problems, however they are considered individually in the other key issues.
What is the expected effect on the cost-effectiveness estimates?	It is unclear whether the relative efficacy of liso-cel is over or underestimated.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on real-world use of liso-cel at second line, on the impact of prior polatuzumab and the efficacy of subsequent recently approved therapies.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 2: Whether to use event-free survival (EFS) or progression free survival on subsequent therapy (PFS2) for economic modelling structure

Report section	3.2.2, 3.2.6
Description of issue and why the EAG has identified it as important	The company uses event-free survival to inform the economic model, however this pools together people who are cured and not cured at third line, introducing bias in favour of liso-cel.
What alternative approach has the EAG suggested?	The EAG prefers to use PFS2 to inform model health states, where people experiencing a PFS2 event are unlikely to be cured, meaning your health states are more homogenous. The EAG prefers a Weibull and log-logistic distribution for liso-cel and SOC respectively.
What is the expected effect on the cost-effectiveness estimates?	Impact of this change alone appears small but it is linked to other model changes.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 3: Choice of extrapolation for overall survival (OS)

Report section	3.2.6.3
Description of issue and why the EAG has identified it as important	The EAG considers the TRANSFORM data to be too immature to provide reliable estimates of cure proportions, as they are inconsistent with follow-up from the ZUMA-7 trial.
What alternative approach has the EAG suggested?	The EAG uses an alternative approach to obtaining OS extrapolations which are consistent with ZUMA-7 and PFS2
What is the expected effect on the cost-effectiveness estimates?	These changes reduces the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	Real-world follow-up of second line liso-cel use would inform the plausibility of current extrapolations.

Issue 4: Choice of extrapolation for time to next treatment (TTNT)

Report section	3.2.6.4
Description of issue and why the EAG has identified it as important	The company's modelling of EFS and TTNT resulted in differing cure proportions. The EAG was unclear why these outcomes would disagree.
What alternative approach has the EAG suggested?	The EAG prefers to use an EFS extrapolation to model TTNT, as it considers the data more mature.
What is the expected effect on the cost-effectiveness estimates?	This change alone increases the cost-effectiveness of liso-cel, however it is also affected by other assumptions of subsequent therapy use.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up from the trial may provide more reliable estimates of TTNT.

Issue 5: Utility value for "healthy" health state for first 5 years of model

Report section	3.2.7
Description of issue and why the EAG has identified it as important	The utility value used by the company comes from TRANSFORM however is high compared to other sources for a similar population.
What alternative approach has the EAG suggested?	The EAG prefers to use a utility value from TA895 for this health state for consistency with other appraisal, and plausibility of value.
What is the expected effect on the cost-effectiveness estimates?	This decreases the QALY gains associated with liso-cel.
What additional evidence or analyses might help to resolve this key issue?	Alternative sources of data may provide additional information on the most appropriate utility value for this health state.

Issue 6: Bridging therapy distribution

Report section	3.2.8.1.2
Description of issue and why the EAG has identified it as important	The company use information from the liso-cel arm of TRANSFORM to inform the proportion of people receiving bridging therapy and the distribution of bridging therapies used to inform their modelling for second and third line CAR T therapy.
What alternative approach has the EAG suggested?	The EAG prefers to use UK specific data to model proportion receiving bridging therapy and the distribution of bridging therapies used prior to CAR T infusion
What is the expected effect on the cost-effectiveness estimates?	Changing to the EAG preferred assumption worsens the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	The availability of line-specific bridging therapy information could further improve the modelling assumptions.

Issue 7: Subsequent therapy distribution

Report section	3.2.8.3
Description of issue and why the EAG has identified it as important	The company use data from TRANSFORM to model the distributions of subsequent therapies, however this does not appear representative of UK NHS care. In particular the high rate of subsequent CAR T in the SOC arm.
What alternative approach has the EAG suggested?	The EAG prefers estimates specific to UK care provided by the company's clinical experts for the distribution of the types of subsequent therapies received, and use information from NHS England to inform use of novel therapies.
What is the expected effect on the cost-effectiveness estimates?	This is the most influential change and liso-cel no longer dominates SOC. Instead liso-cel is more expensive but provides more QALYs, meaning the ICER can be considered.
What additional evidence or analyses might help to resolve this key issue?	Data collection from real-world CAR T use may further enhance the modelling.

Issue 8: Adverse event costs

Report section	3.2.8.5
Description of issue and why the EAG has identified it as important	The company apply the CAR T tariff cost to account for the costs of adverse events in the liso-cel arm which excludes AEs occurring 100 days beyond therapy (i.e. those associated with subsequent therapy), but for SOC they apply the costs of events that occurred in TRANSFORM and also the CAR T tariff cost, potentially double counting.
What alternative approach has the EAG suggested?	The EAG attempts to remove the portion of the tariff cost attributable to AEs when it is applied to third line CAR T, for consistency with the approach for liso-cel.
What is the expected effect on the cost-effectiveness estimates?	Changing to the EAG preferred assumption worsens the cost-effectiveness of liso-cel.
What additional evidence or analyses might help to resolve this key issue?	A breakdown of adverse events by line of therapy would allow for more detailed modelling of AE costs.

1.6 *Other key issues: summary of the EAG's view*

The EAG did not identify any further key issues.

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

Table 2: Summary of EAG's preferred assumptions and ICER

Assumption	ICER(£/QALY)
Company base case	-£29,314 (SOC dominated)
EAG01: Use PFS2 for model health state occupation	-£30,589 (SOC dominated)
EAG02: Weibull distribution used for liso-cel PFS2 and Loglogistic distribution used for SOC PFS-2	-£30,961 (SOC dominated)
EAG03: Discount applied per cycle.	-£27,986 (SOC dominated)
EAG04: log-logistic parameters re-estimated and used for liso-cel & SOC OS	-£23,149 (SOC dominated)
EAG05: log-normal and generalised gamma parameters re-estimated and used for liso-cel and SOC TTNT respectively	-£36,540 (SOC dominated)
EAG06: Bridging therapy changed	-£27,656 (SOC dominated)
EAG07: AE costs removed for 3L CAR T	-£24,130 (SOC dominated)
EAG08: Subsequent therapy changed including proportion in SOC receiving CAR T at 3L	£38,126
EAG09: Utility changed for pre-PFS-2 state	-£26,078 (SOC dominated)
EAG10: Starting age of model changed	-£31,806 (SOC dominated)
Cumulative	£38,638

Table of Acronyms

Acronym	Definition
1L	First-line
2L	Second-line
3L(+)	Third-line (plus)
ABC	Activated B-cell like
ACM	Appraisal committee meeting
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogenic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
Axi-cel	Axicabtagene ciloleucel
BCMA	B-cell maturation antigen
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criterion
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medical Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	Cyclophosphamide, doxorubicin and prednisone
CI	Confidence interval
CII	Cost Inflation Index
CNS	Central Nervous System
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CRR	Complete response rate
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
CUA	Cost utility analysis
DCO	Data cut off
DHAP	Dexamethasone, cytarabine, cisplatin
DHAX	Dexamethasone, cytarabine and oxaliplatin
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Event-free
EFS	Event-free survival
EMA	European Medicines Agency
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study

Acronym	Definition
ESHAP	Etoposide, methylprednisolone, high dose cytarabine and cisplatin
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FISH	Fluorescence in situ hybridisation
FLBCL	Follicular large B-cell lymphoma
GCB	Germinal centre B-cell
GDP	Gemcitabine, dexamethasone and cisplatin
GEMOX	Gemcitabine and oxaliplatin
GP	General practitioner
HCRU	Healthcare resource use
HDCT	High dose chemotherapy
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HMRN	Haematology Malignancy Research Network
HR	Hazard ratio
HRQOL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
HTA	Health Technology Assessment
ICE	Ifosfamide, carboplatin and etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IHC	Immunohistochemistry
INHB	Incremental net health benefit
IPD	Individual patient data
IPI	International Prognostic Index
IRC	Independent review committee
IRR	Infusion Related Reaction
IRT	Interactive Response Technology
ITT	Intention to treat
IVE	Ifosfamide, etoposide and epirubicin
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
LFT	Liver function test
Liso-cel	Lisocabtagene maraleucel
LVEF	Left ventricular ejection fraction
LYG	Life years gained
LYM	Lymphoma
MAIC	Matching adjusted indirect comparison
MAS	Macrophage activation syndrome
MCM	Mixture cure model
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimal Important Difference
MUGA	Multi-gated acquisition scan
MYC	Myelocytomatosis oncogene
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NEC	Not elsewhere classified
NHB	Net health benefit
NHL	Non Hodgkin’s lymphoma
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified

Acronym	Definition
NR	Not reported
ONS	Office for National Statistics
ORR	Overall Response Rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PICO	Population, Intervention, Comparators, Outcomes
PMBCL	Primary Mediastinal B-cell lymphoma
Pola	Polatuzumab
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QOL	Quality of life
R-	Rituximab
RCT	Randomised controlled trial
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SAS	Safety analysis set
SCT	Stem cell transplantation
SD	Stable disease / standard deviation
SE	Standard error
SLE	Systemic lupus erythematous
SLR	Systemic literature review
SMR	Standardised mortality ratio
SOC	Standard of care
STM	State transition model
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
tFL	Transformed follicular lymphoma
THRBCL	T-cell histiocyte rich large B-cell lymphoma
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor
TSD	Technical Support Document
TTNT	Time to next treatment
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

The EAG has reviewed the company submission (CS) from Bristol Myers Squibb (BMS) to NICE on the clinical effectiveness and cost-effectiveness of lisocabtagene maraleucel (liso-cel) for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) or follicular lymphoma grade 3B (FL3B) after first-line chemotherapy in people who are eligible for stem cell transplantation.

Liso-cel is currently licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy but the NICE appraisal of liso-cel in this indication was suspended in November 2021.
The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of approval for liso-cel in April 2023. A marketing authorisation type II Variation extension application to the MHRA was made in December 2023 for the treatment of [redacted].

1.2 *Background*

The company provides a description of liso-cel and of the relevant health condition in sections 1.2 and 1.3 of the company submission (CS). This section provides a critique of the company overview of the disease, the technology, and the positioning of lisocabtagene maraleucel (liso-cel) in the treatment pathway.

1.2.1 Condition, epidemiology and symptoms

The CS cited relevant references in their description of the health condition (B.1.3.1), although the EAG noted that some of the citations were secondary references (e.g. Tilly 2015,[1]) rather than primary studies. Non-Hodgkin lymphoma (NHL) is one of the

most common types of cancer. In England, 10,710 people were diagnosed with NHL in 2020, with an age standardised incidence of 19.7 per 100,000 population.[2] NHL is categorised according to the type of white blood cell affected, B cell or T cell.

Large B-cell lymphomas (LBCL) are one of 12 families of mature B-cell neoplasms. The CS accurately cites HMRN data, estimating that 5,440 people are newly diagnosed with LBCLs each year in the UK, with an annual incidence of 8.3 cases per 100,000 people. LBCL has been classified by The World Health Organization (WHO) into several specific entities.[3, 4] The types that are of interest to the current submission are those that liso-cel is indicated for:

- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
- High-grade B-cell lymphoma (HGBCL)
- Primary mediastinal B-cell lymphoma (PMBCL)
- Follicular lymphoma grade 3B (FL3B)

Due to similarity in treatment pathway at second-line for these four aggressive subtypes of lymphoma, the CS collectively refers to them as LBCL. The EAG clinical experts agree that in clinical practice, DLBCL, PMBCL, HGBCL and FL3B are treated similarly.

In the UK, DLBCL is the most common type of LBCL, accounting for 40% of all NHL cases (approximately 4,870 cases, typically presenting in older adults and characterised by aggressive, heterogeneous clinical features).[5, 6] PMBCL, a rarer type, has an average annual incidence of 0.2 per 100,000 (140 cases per year), affects young adults and women predominantly, and is marked by fast-growing tumours in the mediastinal area.[7]. HGBCL encompasses aggressive lymphomas with specific genetic translocations, including double or triple-hit lymphomas which involve rearrangements of MYC and either BCL2 or BCL6 genes (or both).[8, 9] The CS states that data on HGBCL incidence are scarce but that it is generally considered a rare NHL subtype, citing a secondary reference suggesting it comprises 1–2% of cases.[10] The EAG was unable to verify the incidence data. The CS states HGBCL often presents in elderly patients with widespread disease and high prognostic scores, however the EAG is unable to access the citation to verify this. FL3B, now classified as FLBCL, is a rare subtype of follicular lymphoma.[11]

Follicular lymphoma has an average annual incidence of 3.6 per 100,000 people in the UK, amounting to approximately 2,320 cases per year.[7] The CS also states that FL3B accounts for only 5-10% of these cases and presents similarly to DLBCL, although the citations used by the company are not primary studies and the EAG is unable to verify the proportion of cases. The accuracy of these data has no implications for the results or conclusions of the CS.

Prognostic tools for LBCL involve scoring systems that assess clinical characteristics such as age, presence of B symptoms, performance status, lactate dehydrogenase levels, number of sites involved, and clinical stage.[12] These tools include:

- International Prognostic Index (IPI)
- Revised IPI (R-IPI)
- National Comprehensive Cancer Network-IPI (NCCN-IPI)
- Age-adjusted IPI (aaIPI)
- Secondary age-adjusted IPI (sAAIPI)

The sAAIPI, assessed in a study of patients with aggressive relapsed/refractory (R/R) DLBCL eligible for stem cell transplantation, effectively predicted progression-free survival (PFS) and overall survival (OS) by categorizing patients into low, intermediate, and high-risk groups.[12] According to the CORAL study, the sAAIPI, together with early relapse and prior rituximab exposure, was negatively correlated with the response to second-line treatment and overall survival (OS).[13]

Patients with LBCLs typically present with painless swellings in the neck, armpit or groin caused by enlarged lymph nodes, accompanied by general symptoms (B symptoms) such as fever, night sweats, and significant weight loss.[6] These symptoms significantly impair the health-related quality of life (HRQoL) of patients, as shown by reduced scores across all domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) compared with an age- and sex-matched reference cohort of the general population in a Dutch study using population-based registry data of patients with DLBCL.[14] The current second-line standard of care (2L SOC) involving high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (SCT) further diminishes HRQoL.[15] Severe short- and long-term side effects, such as infections,

cardiac toxicity and secondary tumours are a risk of SCT.[16, 17] Patients undergoing HDCT and SCT have notably poorer physical and mental HRQoL for a median of eight years post-treatment compared with age- and sex-matched controls.[18] The emotional toll is especially high for those with relapsed/refractory (R/R) disease,[19] who experience even greater reductions in HRQoL with subsequent treatment lines.[20] The CS states there is an unmet need for new second-line (2L) treatments to improve patient outcomes and prevent disease progression.

1.2.2 Position of liso-cel in the clinical pathway

First line

The UK treatment pathway for LBLC is outlined in CS Figure 4. First line standard of care for LBCL in UK practice is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) which the company states was used in around 80% of DLBCL patients in 2015. The company cites the National Comprehensive Cancer Network (NCCN) guideline,[21] which the EAG has not been unable to access, however clinical advice to the EAG confirms that this is the most commonly used first-line therapy. There has been some change in first line practice with the 2023 NICE recommendation of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola+R-CHP) for DLBCL. The company reports that their clinical advisors state that most [DLBCL] patients receive Pola+R-CHP, however clinical advice to the EAG is that this isn't necessarily the case for all patients.

CS Figure 3 reports cure rates with first-line treatments to be 60-70% in 2021 and estimates the cure rate in the Pola+R-CHP era to be around 70-80% (although the EAG notes that the company cites a secondary reference and the original data may actually relate to 2014). The EAG clinical advisers agree with these estimates, therefore there are no implications for the results or conclusions of the CS.

Second line

The company focus is on second line treatment for people with R/R LBCL who are eligible for SCT. The CS reports that approximately 50% of people with R/R LBCL are eligible for SCT. The CS only uses secondary sources for these estimates and the EAG hasn't verified the primary sources, however the EAG clinical experts agree 50% is reasonable. The second line treatment pathway for these people is discussed

in CS Section B.1.3.4. The current standard of care (SOC) for SCT eligible people is re-induction therapy with platinum-based immunochemotherapy followed by high dose chemotherapy and SCT in responding people. The choice of reinduction immunochemotherapy varies. The CS reports that their clinical experts most commonly use rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP) and rituximab, ifosfamide, carboplatin and etoposide (R-ICE). The CS report that around half of those eligible for SCT in principle will go on to receive it and of those who do receive it approximately half again experience further relapse. This is outlined in a hypothetical sample in CS Figure 3. The EAG were unable to verify these data in all of the literature cited, for example in Sarkozy 2018[22] the proportion of SCT-eligible patients who received SCT was 40%. However, the EAG clinical adviser concurred that the proportions in CS Figure 3 were reasonable.

Although not currently routine clinical practice, clinical advice to the EAG is that all people who are R/R within 12 months and eligible for SCT receive axi-cel via the Cancer Drugs Fund.

For those not eligible for SCT, CS Section B.1.3.2 reports that for these patients there is no established SOC and treatment can be palliative. Clinical advice to the EAG is that in UK practice these patients will often have another line of salvage chemotherapy. While this is not usually curative, if they relapse or do not respond some may then have 3rd line CAR T therapy without having SCT.

The CS summarises the UK treatment pathway in Figure 4. The anticipated positioning of liso-cel is shown at second-line for those with R/R disease and eligible for SCT.

Third line

Subsequent treatments for those relapsing after current SOC at second line are outlined in CS Section B.1.3.4 and presented in CS Figure 4. The third-line treatment landscape is evolving and the EAG clinical adviser confirmed that the various options for third-line treatment within current SOC are described in the CS, also noting that most people receive CAR T following second line SOC if fit enough. This concurs with the CS experts who estimated between 40-85% would receive axi-

cel. The CS clinical experts anticipated third line treatments following treatment with liso-cel would be bispecific antibodies, mostly glofitamab or epcoritamab. The CS reports the proportions estimated to receive each of these to be 37.5% (range 25-40%), the EAG believes this is a typographical error as CS reference 45 reports rates of 32.5% (which is also used in the health economic model, see CS Table 78).

Overall, the EAG are satisfied that the clinical pathway presented in the CS generally reflects current UK practice.

Unmet need

CS Section B.1.3.5 states that current SOC for those with early R/R LBCL and eligible for SCT is associated with limited survival benefit because, as discussed above, approximately half of people don't receive SCT and half who do experience a further relapse. The CS provides data on event free survival (EFS) rates from SOC arms of three RCTs of second-line treatments, including the pivotal RCT for liso-cel included in the present submission.[23] These rates for EFS were also summarised in CS Table 5, where the EAG notes that only two of the three RCTS reported median EFS. Therefore, the EFS cited for SOC ([redacted] or less) was actually based on two trials, one of which was the liso-cel trial included in the submission. The EAG notes that EFS was 3.0 months in the SOC arm of the BELINDA trial.[24] Although there are a range of factors to consider in these estimates, they appear reasonable to the EAG clinical advisers.

The CS also describes that people who receive SCT as current SOC may experience both short term toxicity during the treatment phases but also longer-term adverse effects which can have a negative impact on quality of life. The EAG clinical advisers note that there can be significant effects on quality of life as a person starts second-line treatment, however this is irrespective of the type of treatment. On checking the citations provided by the CS[15-18, 20] the EAG generally concurs that the evidence provided supports the claim of adverse events and quality of life effects from SCT, but notes that these data were not specific to SCT at second-line treatment for R/R LBCL.

The CS makes their case that liso-cel can address the current unmet need of people with R/R LBCL from meaningful improvements in clinical outcomes and a favourable safety profile, summarising key results from the TRANSFORM trial, the pivotal trial for the appraisal, which is summarised in Section 2.2 below.

1.3 *Critique of company's definition of decision problem*

The EAG's comments on the company's decision problem can be seen in Table 3. There are some differences between the company decision problem and the final NICE scope but the EAG has no major concerns. The evidence provided in the submission for liso-cel is aligned with the decision problem population.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with relapsed or refractory aggressive B-refractory DLBCL, HGBCL, PMBCL or FL3B after 1 prior therapy	Adults with early (≤ 12 months) relapsed/primary refractory DLBCL, PMBCL, HGBCL or FL3B who are eligible for SCT	The population included in the final scope is broader than the TRANSFORM trial in the following two aspects: • Only patients with early relapsed (within 12 months)/primary refractory disease are included in TRANSFORM, in line with license for liso-cel • Only patients eligible for SCT enrolled in the TRANSFORM trial The population considered for this submission is therefore narrower than the NICE final scope. This represents a subpopulation of the anticipated licensed indication in order to align with the population included in the pivotal TRANSFORM trial, which enrolled only patients who were eligible for SCT and had early relapsed/primary refractory disease. Liso-cel is also being evaluated for the treatment of relapsed or refractory (R/R) LBCL patients	The EAG agrees that this narrower population represents a subgroup of the relevant patient population and that the clinical evidence in the TRANSFORM trial matches the population in the decision problem. There is no uniform definition for eligibility for SCT and the EAG clinical advisers confirm that this can vary across the UK. At clarification it was confirmed to the EAG that the TRANSFORM trial did not include any specific definition regarding eligibility for SCT (see Section 2.2.2 for further discussion).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			who are ineligible for HDCT and ASCT (SCT-ineligible) in the Phase II trial TRANSCEND-PILOT (NCT03483103).[25] This population is not included in this submission and will be appraised separately, in order to align this submission with the population included in the TRANSFORM trial and licence for liso-cel in this indication.	
Intervention	Lisocabtagene maraleucel	Lisocabtagene maraleucel	In line with the NICE final scope.	The EAG agrees that the intervention is in line with the NICE scope. Liso-cel is currently indicated for the treatments of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy and a marketing authorisation type II Variation extension application to the MHRA for a license in Great Britain was made in December 2023. Liso-cel is anticipated to be indicated for the treatment of: • [redacted]
Comparator(s)	Established clinical management without	SOC re-induction therapy (R-DHAP [rituximab,	There are several re-induction therapies available in the UK. In	Although advice to the EAG is that SOC regimens are generally

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	lisocabtagene maraleucel, including but not limited to: • Immunotherapy with HDCT with or without ASCT Polatuzumab vedotin with rituximab and bendamustine (Pola+BR; if haematopoietic stem cell transplant is not suitable)	dexamethasone, cytarabine, cisplatin], R-ICE [rituximab, ifosfamide, carboplatin, etoposide], R-GDP [rituximab, gemcitabine, dexamethasone, cisplatin]) followed by HDCT and ASCT in responders	this appraisal, only R-DHAP, R-ICE and R-GDP are considered as relevant comparators, as these regimens are deemed the most routinely or commonly used in UK clinical practice, according to feedback received from UK clinical experts. Additionally, as the population for this submission is patients who are eligible for SCT, Pola+BR is not considered a relevant comparator as it is licensed for those who are not suitable for ASCT (TA649).	centre-specific and the use of R-DHAP is low, the EAG agrees that the SOC regimens included in the comparator are those most commonly used in UK clinical practice, and that SOC is the appropriate comparison for the restricted population (those eligible for SCT) in the company decision problem.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • event-free survival • response rates • adverse effects of treatment • health-related quality of life	All outcomes specified in the NICE final scope are included in the submission as follows: • event-free survival (time from randomisation to death from any cause, progression, failure to achieve complete response or partial response by 9 weeks post-randomisation or start of new antineoplastic therapy	Event-free survival (EFS) is the primary endpoint from the TRANSFORM trial.[26] For early relapsed/primary refractory LBCL, this endpoint is more clinically relevant than progression-free survival (PFS) given the curative intent of treatment. In this indication, 'stable disease' is not considered a successful treatment outcome and, therefore, patients who remain progression-free but with stable disease are moved on to receive a subsequent treatment line. In TRANSFORM, these	The EAG agrees that the outcomes presented reflect those in the NICE final scope. Clinical expert advice to the EAG is that there is no standard definition of EFS and that EFS is not a validated end-point in clinical trials, but that the rationale for the definition used in the TRANSFORM trial is reasonable. The EAG clinical advisers also agreed that EFS is a more appropriate outcome than PFS, agreeing that stable disease is not considered a successful outcome.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		due to efficacy concerns, whichever occurs first) • overall survival (time from randomisation to time of death due to any cause) • progression-free survival (time from randomisation to progression, or death from any cause, whichever occurs first) • progression-free survival on next line of therapy (time between randomisation to progressive disease on the next line of subsequent treatment or death from any cause) • response to treatment, including: ○ complete response rate (percentage of patients achieving a complete response) ○ duration of response (time from first response to disease progression,	patients could crossover into the liso-cel arm and, as a result, any comparison of progression-free survival between liso-cel and standard of care is likely to be biased. In line with the approach taken in TA895, EFS will therefore be used alongside overall survival (OS) and health-related quality of life (HRQoL) data to capture the most important health related benefits of liso-cel in the cost-effectiveness modelling.[27]	The EAG considers that the additional, non-scoped outcome of progression-free survival on next line of therapy (PFS2) is important. This outcome includes the impact of subsequent therapies received and the EAG argues that as people receive potentially curative therapies at third line, PFS2 may be a better outcome from which to derive health states for the cost-effectiveness modelling. This is discussed in more detail in Section 3.2.6.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		start of new antineoplastic therapy due to efficacy concerns or death from any cause) ○ overall response rate (percentage of patients achieving an objective response of partial response or better) • adverse effects of treatment health-related quality of life using the global health/quality of life, fatigue, physical and cognitive functioning subscales of the EORTC QLQ-C30, the FACT-LymS and EQ-5D		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost	• The cost-effectiveness of liso-cel versus SOC has been evaluated, in line with the NICE reference case • A lifetime horizon has been adopted within the analysis to sufficiently reflect any differences in costs between the	In line with the NICE final scope	The EAG agrees that the cost-effectiveness of liso-cel addressed in the CS has been evaluated in line with the NICE reference case and is appropriate for this appraisal.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	technologies being compared • Costs were considered from an NHS and Personal and Social Services perspective (PSS) A patient access scheme (PAS) for liso-cel was included in the analysis		

ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; EFS: Event-free survival; FL3B: follicular lymphoma grade 3B; HDCT: High-dose chemotherapy; HGBCL: high grade B-cell lymphoma; HRQoL: health-related quality of life; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; R/R: relapsed/ refractory; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; SOC: Standard of Care; SCT: stem cell transplant.

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The EAG reviewed the methods used by the company to assess the eligibility criteria, identify, extract, assess risk of bias and synthesise the evidence on the safety and efficacy of treatment for patients who are SCT-eligible with R/R LBCL receiving 2L treatment. A range of study types from RCTs to observational studies were included. The review initially included various global therapies; this was then refined to focus on the NICE decision problem as discussed further below.

2.1.1 Searches

The searches were conducted in October 2017 and updated and re-ran six times, most recently in February 2024. The original Medline and Embase searches were searched via the ProQuest platform, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid and the Database of Abstracts of Reviews of Effects (DARE) were searched via the Centre for Reviews and Dissemination (CRD) database (CS Appendix D.1.1.1 Table 10). Conference proceedings were searched across eight conference websites in March 2023 and February 2024. Six conference websites (with the addition of the European Organisation for Research and Treatment of Cancer (EORTC) and the International Workshop on non-Hodgkin Lymphoma (iwNHL) in the March 2023 and February 2024 SLR update were searched in April 2019 and October 2017 (CS Appendix D.1.1.2 Table 12, Table 13 and Table 14). Three clinical trials registries were searched in March and December 2023. The search terms are provided but the numbers of results and included studies are not reported. The numbers of search results reported in the PRISMA flow diagrams from the 'Identification of new studies via other methods' indicates broad searches were carried out (CS Appendix D.2 Figure 1 and Figures 2-6 supplied in the CS Clarification response). It is also not reported if a date limit was applied to these searches. Not applying a date limit to the search carried out in March 2023 would be optimal, as the registers were not reported to have been searched in April 2019 or October 2017 (CS Appendix D.1.1.2 Table 14 and Figure 6: Combined PRISMA diagram for the October 2017 clinical SLR, including subsequent update in 2019).

Systematic reviews were sought from additional database searches and the bibliographies of included studies were hand-searched to identify further reports (CS Appendix D.1.1 Hand searches). Search terms for the concepts related to refractory disease are omitted, such as drug resistance, salvage therapy or treatment failure. The Medline, Embase and Cochrane Library searches contain a restricted amount of exploded indexing terms (MeSH and Emtree), which would result in the narrower indexing terms not being searched, thus limiting the sensitivity. The Medline (MeSH) and Embase (EMTREE) indexing terms for study types contains mainly EMTREE terms and a large proportion of MeSH terms are not included in the search. The free-text search terms contain limited and inconsistent use of truncation and adjacency operators. The free text searches were also not searched in fields beyond the Title or Abstract. Searching in the 'Keywords/identifiers (IF)', 'Subjects (SU)' or 'Anywhere except full text (NOFT)' fields would have increased the comprehensiveness of the search (CS Appendix D.1.1.1 Electronic database search terms - Table 9: Search terms used for database searches (Embase, Medline) (via ProQuest) – April 2019 and October 2017 SLRs combined).

The update searches from July 2020 onwards are significantly more comprehensive and well-constructed (CS Appendix D.1.1.1 Tables 8-1). The searches contain database-specific indexing and free-text terms, including keywords. However, the search was only run for records added to databases from April 2019 onwards. The EAG believe that the update search should not have been limited to this date, given the major changes that were applied; therefore, the search is not a true update of the original and potentially eligible studies published prior to 2019 may have been missed. The update search focusses on the population/ condition (R/R DLBCL) and study type only. Not including terms for the intervention increases the sensitivity of the searches. Language or publication format limits were not applied. The search field 'Publication type' (.pt) was not included in the search lines for study type for randomized controlled trials, clinical trials or observational studies from the Medline search study type filters (CS Appendix D.1.1.1 Tables 1, 2, 3, 5 and 7 lines 12-16), which may have resulted in a small number of studies being missed.

The search terms used for searching the grey literature and conference sources are provided but the numbers of retrieved and included results are not (CS Appendix D.1.1.2 Tables 12, 13 and 14). Full details of the reviews, guidelines and grey

literature examined in the hand-searches are also not reported (CS Appendix D.2 Search results). Only conference proceedings from 2016 onwards were searched. A search of older conference proceedings may have identified further trials that were never published, to counter publication bias.

The EAG had some concerns about the reporting of the search figures, due to discrepancies in numbers of results reported in the search strategy and the PRISMA diagrams provided in the company clarification response. For example, there are 464 Medline results reported in the search strategy in Appendix Table 2 and 506 in the PRISMA flow diagram (Figure 2 CS Clarification response A24).

124 articles were included in the updated searches and reported in the CS appendix. The EAG note some discrepancies in the reasons for exclusions in the CS appendix. The company clarified (clarification question A5) that, the reasons for exclusion were 'incomplete' or 'insufficient data' when they lacked clear information on prior lines of treatment, had unknown treatment lines, mixed treatment lines without subgroup data, mixed histologies without subgroup data, or combined both mixed treatment lines and histologies. Additionally, studies were excluded for 'other' reasons such as having few eligible patients, being protocols with no results, or not being relevant to the topic of the SLR. The EAG consider that the reasons provided are reasonable. The CS only included one article as being relevant for the decision problem.

2.1.2 ROBIS Assessment of company SLR

A summary of the EAG's quality assessment of the company's systematic literature review (SLR) using the ROBIS tool is presented in Appendix 1. The EAG has some concern over the risk of bias. There is concern regarding the original search strategy and restrictive update searches and also issues over the application of the screening against the eligibility criteria. The EAG checked all included and excluded studies and found that these were all in line with the eligibility criteria, however, there was some disagreement on the reasons for exclusion. Only one study originally identified by the SLR was eventually included in the CS but the criteria used to assess eligibility of the other studies were not explicit. The EAG consider that it was

appropriate that no indirect comparison was conducted as the CS only included one head-to-head comparison to inform the clinical evidence.

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

2.2.1 Overview

The source of evidence for the assessment of clinical effectiveness of liso-cel for people with LBCL who have relapsed within 12 months or are refractory to first line immunochemotherapy, and are eligible for ASCT, is from a single RCT, the TRANSFORM trial (NCT03575351). The CS presents data from the final data-cut off (DCO) dated October 2023, with a clinical study report (CSR) from an earlier DCO (May 2022) also provided in the company's reference pack. The main publication for TRANSFORM, Abramson 2023,[26] reports the DCO of May 2022 for the primary analysis. Further details of the planned interim analyses of TRANSFORM are given in CS section B.2.6.1.

TRANSFORM is an open-label parallel-group Phase III multinational RCT conducted in 11 countries across Europe and the USA, comparing liso-cel with SOC. A summary of the trial design is presented in CS Figure 5, and a summary of TRANSFORM methodology with cross-references to the relevant sections in the CS where more detail can be found is presented in Table 4. Further description is below.

Table 4: Summary of TRANSFORM methodology

Method step	Summary details	Section(s) of CS of relevance or other source
Method of randomisation	Permuted-blocks method with a dynamic block size.[a] Stratified by response to first line (1L) therapy	B.2.3.1

	(refractory versus relapse)[b] and sAAIPI (0–1 versus 2–3). Interactive response technology.	

Eligibility criteria	• Aged 18–75 years
	• Eligible for ASCT
	• LBCL:
	  ○ DLBCL not otherwise specified (NOS), de novo or transformed from indolent NHL
	  ○ HGBCL with rearrangements of MYC and either BCL2, BCL6, or both with DLBCL histology
	  ○ PMBCL
	  ○ T-cell histiocyte rich LBCL (THRBCL)
	  ○ FL3B
	• Refractory disease (SD, PD, PR or CR with relapse ≤ 3 months) or relapsed disease (CR with relapse ≤ 12 months), to CD20 antibody and anthracycline containing first-line therapy
	• ECOG performance status of 1 or less
	• Adequate organ function (definitions provided)
	• PET-positive disease as per Lugano 2014 criteria[28]
		B.2.3.1, Table 7

Trial drugs by period of study	Liso-cel arm: bridging therapy if needed (R-DHAP, R-ICE or R-GDP), followed by lymphodepleting chemotherapy and liso-cel. SOC arm: three cycles of re-induction therapy (R-DHAP, R-ICE or R-GDP) followed by HDCT and ASCT in those responding. Participants meeting specific criteria could crossover to liso-cel.	B.2.3.1, Table 7

Primary endpoints of relevance to the decision problem	Event free survival (EFS), defined as time from randomisation to progression, failure to achieve CR or PR by 9 weeks, start of a new antineoplastic therapy due to efficacy concerns or death from any cause, whichever occurs first, based on IRC assessment	Table 7
Key secondary endpoints of relevance to the decision problem	Key secondary objectives: • Complete response rate (CRR) • Progression-free survival (PFS) • Overall Survival (OS) Other secondary objectives: • Duration of response (DOR) • Overall response rate (ORR) • PFS on next line of treatment (PFS-2) • Adverse events (AE) • Serious adverse events (SAE) • Health-related quality of life (HRQoL) Efficacy endpoints were based on IRC assessment	Table 7
Statistical analysis	Efficacy analyses used the ITT analysis set, and the safety analysis set was used to analyse safety. A hierarchical testing strategy was used for the primary and key secondary endpoints. The O'Brien-Fleming boundary alpha spending function was used to adjust for multiplicity. EFS (primary outcome) was analysed with a stratified Cox proportional hazards model. Kaplan-Meier product limit was used for time-to-event end points; time-to-event rates were computed using	B.2.4, Table 11, Table 12

	the Greenwood formula. HRs were estimated using a stratified Cox proportional hazards model. For OS, as patients from the SOC arm had the possibility to crossover to liso-cel, a 2-stage Weibull approach (2-stage accelerated failure time model), and a rank-preserving structural failure time model were investigated as supportive analyses. A Cochran-Mantel-Haenszel test with stratification factors as strata was used for CRR.	

1L: first line; ASCT: autologous stem cell transplant; CR: Complete response; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL3B: follicular lymphoma grade 3B; HDCT: High-dose chemotherapy; HGBCL: high grade B-cell lymphoma; ITT: Intention to treat; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; MYC: Myelocytomatosis oncogene; NHL: non-Hodgkin Lymphoma; NOS: not otherwise specified; PET: positron emission tomography; PD: Progressive Disease; PMBCL: primary mediastinal B-cell lymphoma; PR: Partial Response; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: rituximab, gemcitabine, dexamethasone & cisplatin; R-ICE: rituximab, ifosfamide, carboplatin; etoposide; sAAIPI: secondary age-adjusted International Prognostic Index; SD: Stable Disease; SOC: Standard of Care; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma.

[a] Block size of 4 with probability of 0.75 and block size of 6 with probability of 0.25.

[b] Refractory = stable disease, progressive disease, partial response or complete response with relapse before 3 months; relapse = complete response with relapse on or after lasting at least 3 months.

2.2.2 Eligibility criteria

The population in TRANSFORM is aligned with the population considered in the company's decision problem, which is narrower than the anticipated marketing authorisation and NICE scope (section 1.3). TRANSFORM included adults aged 18 to 75 years with LBCL who have relapsed within 12 months or are primary refractory to first line immunochemotherapy, and are eligible for ASCT. Eligibility for ASCT at the point of study entry was not defined in the trial protocol. In clarification A1, the company explained that TRANSFORM did not include any specific definition regarding eligibility for ASCT, but that the inclusion criteria specified that patients must be aged ≤75 years, have Eastern Cooperative Oncology Group (ECOG)

performance status ≤1 and have adequate organ function (see CS Table 7 for details). Eligibility for ASCT varies across the UK, but generally patients must be fit enough to receive platinum chemotherapy and have a sufficient enough response to proceed to ASCT. ASCT is usually only offered to patients under the age of 70 years, who must have adequate cardiac and renal function and be physically robust. In TRANSFORM, the definition of adequate organ function included creatinine clearance greater than 45 ml /min and left ventricular ejection fraction (LVEF) greater than >40% (see CS Table 7 for definitions of adequate organ function). In the UK, most centres would stipulate a creatine clearance greater than 50 to 60 ml/min and a LVEF greater than 45 to 50%, but this can vary. Specifically, the following types of LBCL were eligible:

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

2.2.3 Interventions

Leukapheresis

All participants underwent leukapheresis prior to randomisation, and liso-cel manufacturing was performed for patients in both arms to enable rapid liso-cel infusion in cases of SOC failure. In Clarification A2, the company explained that in the case of a technical issue where the product could not be used (e.g. due to contamination or manufacturing failure), the patient could have a second collection procedure performed. A second leukapheresis procedure was required to manufacture liso-cel in [redacted] patients randomised to the liso-cel arm and treated with liso-cel, and in [redacted] patients randomised to the SOC arm who subsequently crossed over and were treated with liso-cel.

Liso-cel arm

Participants in the liso-cel arm received bridging therapy if needed, followed by lymphodepleting chemotherapy (LDC) and liso-cel:

- Bridging therapy was allowed for disease control during manufacture of liso-cel (after leukapheresis and prior to LDC) if deemed necessary by the investigator, using one cycle of one of the protocol-defined SOC regimen (see below). Local radiation was allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lesions were present. Bridging therapy is commonly used in NHS practice.[27]
- LDC consisted of cyclophosphamide and fludarabine administered for three days.
- Liso-cel was administered as two sequential IV infusions of CD8+ and CD4+ CAR T cells at a total target dose of 100 × 10^6 CAR T cells 2 to 7 days after completion of LDC. Liso-cel infusion was planned to occur 29 days +/-7 days after randomisation. The actual median time from randomisation to liso-cel infusion was [redacted] days (Clarification A2).

SOC arm

Participants in the SOC arm received re-induction therapy followed (if responded) by HDCT and ASCT:

- Re-induction therapy involved three cycles of one of three permitted SOC regimens (R-DHAP, R-ICE and R-GDP, see CS Table 7 for dose details). The EAG clinical experts considered the SOC regimens in TRANSFORM to be widely used in UK practice, with the choice of regimen depending on the preference of the centre. A switch within these SOC regimens was allowed in the event of toxicity or non-satisfactory response to the selected SOC regimen according to investigator judgement (this was not considered an EFS event). The CSR shows that [redacted]
- [redacted] (‘other’ was not defined). Although one EAG clinical expert considered these proportions and reasons for switching SOC to be reasonable, a second EAG expert noted that in the UK switching due to an suboptimal result would not occur as there is no

evidence to show superiority of one regimen over another, and that instead patients would be referred to third line CAR T. Switching would occur due to toxicity, but the proportion switching in TRANSFORM for this reason is slightly higher than expected. Participants who responded to re-induction therapy had one cycle of HDCT and ASCT.

Participants in the SOC arm could cross-over to liso-cel on request of the investigator if they met the criteria for LDC and liso-cel and if one of the following criteria was confirmed by the Independent Review Committee (IRC). There are no details in the CS or trial protocol regarding how often the IRC met to discuss each case. The criteria for eligibility of crossover were:

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

The company confirmed that there is no record of reasons why patients were not deemed eligible for crossover by the IRC (Clarification A8). Of the 61 patients in the SOC arm who were approved for crossover, the reasons were progression in [redacted], relapse in [redacted], and suboptimal response in [redacted] (Clarification A8). (Note that CS p108 states 60 patients in the SOC arm received liso-cel as a crossover treatment, however in Clarification A9 the company stated that 57/61 actually received liso-cel, with one further person receiving non-conforming product).

Non-conforming liso-cel product and second leukapheresis

In TRANSFORM, one participant in the liso-cel arm and one participant in the SOC arm who crossed over received a non-conforming liso-cel product. Non-conforming product occurs when the manufacture of liso-cel is attempted but is out of specification and so is not referred to as ‘liso-cel’. After careful expert consideration, non-conforming product may be used if it is thought to be in the best interests of the patient. The process for the decision to administer a non-conforming product was outlined in Clarification A3. The company stated that the time to infusion of the non-

conforming product was in line with that for those receiving a conforming product. For commercially-available liso-cel, the company described the process in the EU for managing non-conforming products, and stated that the process in the UK is still being established. The median turnaround time in days (from apheresis to qualifying product release) for out-of-specification liso-cel in Europe over the past 12 months is presented in Clarification 3 Table 1.

Additionally, five patients (3 liso-cel, 2 SOC) required a second leukapheresis for the successful manufacture of liso-cel. In practice, this delays patient access to treatment. The extent and impact of non-conforming product and repeat leukapheresis remains unclear of in real world use of liso-cel.

2.2.4 Risk of bias

The company assessed the risk of bias of TRANSFORM using the minimum criteria recommended by NICE (CS Table 13, CS Appendix 24). There are differences between the company's judgements in CS Table 13 and those in CS Appendix 24 for adequate random sequence generation, concealment of allocation, similarity of prognostic factors and imbalances in dropouts. In addition, it appears that the company confused concealment of treatment allocation with blinding of assigned interventions during the trial. The EAG therefore conducted an independent assessment of risk of bias using Cochrane RoB 2 criteria (Appendix 2). The EAG judged TRANSFORM to have a high risk of bias overall because of the risk of bias due to deviations from the intended interventions inherent in the design of TRANSFORM.

2.2.5 Baseline characteristics

A total of 184 people were randomised, with 92 participants in each arm. A CONSORT diagram is presented in CS Appendix Figure 2, with details of participant disposition tabulated in CS Appendix Table 71 and discussed under CS B.2.3.2. In the liso-cel arm, 89 participants received liso-cel and one participant received a nonconforming product. There was one study drug manufacturing failure and one participant withdrew consent before receiving liso-cel. In the SOC arm, 91 participants started SOC treatment. Of these, 61 (66.3%) patients were approved for switching to liso-cel treatment and 57 received liso-cel (plus one received a non-conforming product). See section 2.2.7 for further discussion on switching.

The CS presents demographic characteristics in CS Table 8 and disease characteristics in CS Table 9. Key characteristics from these are summarised in Table 5 below. The CS describes the demographic characteristics as 'reasonably well-balanced', however the EAG notes that the SOC arm had a higher proportion of patients aged under 65 years (liso-cel 60.9%, SOC 72.8%), with ECOG PS 0 at screening (liso-cel 52.2%, SOC 62.0%), (but not in ECOG PS at baseline, Table 5, suggesting some patients in the SOC arm worsened during the 28 day screening period), and who were men (liso-cel 47.8%, SOC 66.3%). The implications of this are not clear and the imbalances may be to chance. The CS reports that 'generally', UK clinical experts stated that the baseline demographic characteristics of patients in the TRANSFORM trial were aligned with those of patients in UK clinical practice. The EAG notes that both race and ethnicity were not reported by one quarter of participants.

The majority of participants had DLBCL NOS (liso-cel 57.6%, SOC 54.3%). Only 9.2% of all participants had PMBCL, five participants had THRBCL, and one participant had FL3B. Three quarters of participants were refractory to prior treatment, and one quarter of participants had relapsed disease.

In the liso-cel arm 58 (63.0%) participants received bridging therapy, in the SOC arm [redacted] of the participants who crossed over received bridging therapy (Clarification A13).

Table 5: **Key baseline characteristics**

Number of treated patients, n (%)	**Liso-cel (n=92)**	**SOC (n=92)**
Age, median (range: min, max)	60.0 (20, 74)	58.0 (26, 75)
Age category (years)		
<65 years	56 (60.9)	67 (72.8)
≥65 to <75 years	36 (39.1)	23 (25.0)
≥75 years	0	2 (2.2)
Male (at birth)	44 (47.8)	61 (66.3)
Race		
White	54 (58.7)	55 (59.8)
Asian	10 (10.9)	8 (8.7)

Black or African American	4 (4.3)	3 (3.3)
Not reported	22 (23.9)	25 (27.2)
Ethnicity		
Hispanic or Latino	3 (3.3)	3 (3.3)
Not Hispanic or Latino	65 (70.7)	62 (67.4)
Not reported	24 (26.1)	26 (28.3)
Unknown	0	1 (1.1)
ECOG performance status at screening		
0	48 (52.2)	57 (62.0)
1	44 (47.8)	35 (38.0)
ECOG performance status at baseline		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Hematopoietic cell transplantation-specific comorbidity index, median (Min, max)	[redacted]	[redacted]
Disease type at trial entry		
DLBCL	60 (65.2)	58 (63.0)
DLBCL NOS de novo	53 (57.6)	50 (54.3)
DLBCL from transformed indolent NHL	7 (7.6)	8 (8.7)
FL3B	1 (1.1)	0
HGBCL	22 (23.9)	21 (22.8)
PMBCL	8 (8.7)	9 (9.8)
THRBCL	1 (1.1)	4 (4.3)
Time from initial diagnosis to randomisation (months), median	7.57	7.72
sAAIPI at screening - n (%)		
0 or 1	56 (60.9)	55 (59.8)
2 or 3	36 (39.1)	37 (40.2)
Prior response status - n (%)		

Refractory	67 (72.8)	70 (76.1)
Relapse	25 (27.2)	22 (23.9)
Prior chemotherapy response status - n (%)		
Chemorefractory	26 (28.3)	18 (19.6)
Chemosensitive	66 (71.7)	74 (80.4)
Ann Arbor stage - n (%)		
Stage I	8 (8.7)	14 (15.2)
Stage II	16 (17.4)	15 (16.3)
Stage III	18 (19.6)	13 (14.1)
Stage IV	50 (54.3)	50 (54.3)

ECOG: Eastern Cooperative Oncology Group; liso-cel: lisocabtagene maraleucel; SOC: standard of care.
Source: CS Table 8, CS Table 9.

Prior chemotherapy regimens

In response to Clarification question A10, the company provided data on prior chemotherapy regimens. Participants received a wide range of chemotherapy regimens ([redacted] different regimens), with most regimens received by only one or two patients (data not tabulated here). The most frequently used regimens (used by at least 5% of either arm) are presented in Table 6. The most commonly used regimen was cyclophosphamide / doxorubicin / prednisone / rituximab / vincristine (liso-cel [redacted]), followed by cyclophosphamide / doxorubicin / etoposide / prednisone/ rituximab / vincristine (liso-cel [redacted], SOC [redacted]). No prior polatuzumab therapy was received by any participants in TRANSFORM.

Table 6: Prior anti-cancer therapies used by ≥5% of either arm, ITT set

Regimen, n (%)	**Liso-cel n = 92**	**SOC n = 92**
Systemic anti-cancer therapy	[redacted]	[redacted]
Cyclophosphamide/doxorubicin hydrochloride/prednisone/ rituximab/vincristine sulfate	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/etoposide/methotrexate/ prednisone/rituximab/vincristine	[redacted]	[redacted]

Cyclophosphamide/doxorubicin/etoposide/prednisone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisolone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisolone/ rituximab/vincristine sulfate	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisone/ rituximab/vincristine	[redacted]	[redacted]
Cyclophosphamide/doxorubicin/prednisone/ rituximab/vincristine sulfate	[redacted]	[redacted]

2.2.6 Concomitant medications

CS Table 10 reports concomitant medications. These are generally balanced between groups, apart from antiparasitic products, insecticides and repellents, which were much higher in the liso-cel arm (liso-cel [redacted], SOC [redacted]). This classification includes drugs used to reduce the risk of pneumocystis pneumonia, a fungal infection of the lung, which is thought to persist for longer post CAR T than post ASCT.

Concomitant antineoplastic and immunomodulating agents

In response to Clarification question A14, the company provided data on use of concomitant antineoplastic and immunomodulating agents during TRANSFORM. Medications used in more than 5% of either arm are presented in Table 7. Both arms show substantial use of concomitant antineoplastic and immunomodulating agents (liso-cel [redacted], SOC [redacted]), with filgrastim being the most commonly used (liso-cel [redacted] SOC [redacted]). There were imbalances between arms for some of the medications, including filgrastim-sndz (liso-cel [redacted], SOC [redacted]), pegfilgrastim (liso-cel [redacted], SOC [redacted]), and tocilizumab (liso-cel [redacted], SOC [redacted]).

Table 7: Concomitant medication: Antineoplastic and immunomodulating agents used by ≥5% in either arm, safety analysis set.

Drug class, n (%)	Liso-cel, n=92	SOC, n=91
Antineoplastic and immunomodulating agents	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]
Filgrastim-sndz	[redacted]	[redacted]
Granulocyte colony stimulating factor	[redacted]	[redacted]
Lenograstim	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Pegfilgrastim	[redacted]	[redacted]
Pegfilgrastim-cbqv	[redacted]	[redacted]
TBO filgrastim	[redacted]	[redacted]
Tocilizumab	[redacted]	[redacted]

2.2.7 Subsequent treatments

In response to Clarification question A11, the company provided data on use of subsequent anti-cancer therapies in TRANSFORM. At least one subsequent anticancer therapy was received by [redacted] of the liso-cel arm compared with [redacted] of the SOC arm (Table 8). Systemic anti-cancer therapy was more common in the liso-cel arm than the SOC arm ([redacted] vs. [redacted]). As noted elsewhere (see section 2.2.5), a high proportion (65.2%) of the SOC arm crossed over to liso-cel, though [redacted]. Stem cell transplant was more frequent in the liso-cel arm than SOC ([redacted] vs. [redacted]), and radiation therapy was used only in the liso-cel arm ([redacted]). As the company notes in Clarification A11, participants received a wide range of subsequent chemotherapy regimens, with most regimens received by only one or two patients (data not tabulated here). The most commonly used regimen was bendamustine/polatuzumab vedotin/rituximab (liso-cel [redacted], SOC [redacted]).

Table 8: Subsequent anti-cancer therapies, ITT set

Drug type, n (%)	Liso-cel n = 92	SOC n = 92
Subjects with at least one subsequent anti-cancer therapy	[redacted]	[redacted]
Systemic anti-cancer therapy	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]
Autologous	[redacted]	[redacted]
Allogeneic	[redacted]	[redacted]
Radiation therapy	[redacted]	[redacted]
Cancer surgery	[redacted]	[redacted]
Cross over to Liso-cel	n/a	60 (65.2)
Other CAR T	[redacted]	[redacted]
Total Number of Subsequent Systemic Therapies Received (excluding CAR T, radiotherapy and SCT)	[redacted]	[redacted]

2.2.8 Clinical Results

The design of the TRANSFORM trial meant that people in the SOC arm were eligible to cross-over and receive liso-cel if they failed to achieve CR or PR after 3 cycles of SOC, if they progressed at any time, or needed to start a new antineoplastic therapy due to lack of CR at 18 weeks.

For some outcomes, this either led to people being censored from the respective analysis meaning the remaining sample is unbalanced, or people were not censored meaning the benefit from crossover being included in the analysis. Whilst the CAR T therapy is available on the NHS at 3rd line replicating the crossover, in the TRANSFORM trial people crossing over received it slightly quicker than in real-world use due to the manufacturing process occurring whilst they were receiving 2nd line SOC. Hence both approaches introduce bias into the analysis. The EAG requested some alternative analyses exploring the impact of varying the censoring rules.

The TRANSFORM trial recruited 184 people based on a hierarchical testing design. The null hypothesis for the primary endpoint EFS was tested first, and if rejected sequential testing was performed on CRR, PFS and OS.

The results of this submission come from the final efficacy analysis (data-cut October 2023), which contains over a year additional follow-up from the primary planned analysis (May 2022) and were published in Abramson 2023.[26]

Disease evaluations were performed at week 9 and week 18. At week 9, participants had received 3 cycles of SOC, or were 5 weeks post infusion of liso-cel. At week 18, participants were either 8 weeks post the start of HDCT or 14 weeks post liso-cel infusion.

A summary of results is provided in Table 9, however each outcome is discussed in more detail in the following sections.

Table 9: Summary of results from TRANSFORM[26]

	Primary Analysis	Final Data Cut [HR or RR (95% CI)])	EAG alternative analysis
Event Free Survival	0.36 (0.24, 0.52)	[redacted]	(no change)
CRR	1.70	[redacted]	N/A
ORR	1.78	[redacted]	N/A
PFS IRC	0.40 (0.26, 0.62)	[redacted]	[redacted]
PFS2	NR	[redacted][a]	N/A
OS	0.72 (0.44, 1.18)	[redacted]	N/A

a: the EAG is unclear exactly what analysis this point estimate relates to.

2.2.8.1 Primary Outcome - Event Free Survival

The primary outcome and other time-to-event outcomes were analysed using a stratified Cox model, stratified by the trial randomisation strata. In the company's analysis, EFS was defined as the time until progressive disease, or failure to achieve CR or PR at 9 weeks, or beginning a new antineoplastic therapy due to lack of CR, or death. People could be censored in this analysis if they failed to proceed to HDCT/ASCT, if no follow-up data was available, if they began a new antineoplastic therapy without lack of CR or at the last evaluation point is no event was observed. No p-value was provided for this outcome from the most recent data-cuts as significance was achieved during interim analysis 3, with a one-sided p-value < 0.0001 showing liso-cel superiority, as shown in Figure 1.[29] EFS is carried into the company's economic modelling to derive health states. The EAG notes that the company report in the cost-effectiveness section that the assumption of proportionality is violated for EFS. This means the hazard ratio may not give a reliable estimate of relative effect, however the EAG does not contest that a EFS benefit for liso-cel is clear.

Figure 1: Kaplan-Meier Plot for Event Free Survival from Transform Study (taken from Figure 6 of Company Submission)

EFS events were most commonly due to disease progression ( ) and failure to achieve at least PR by 9 weeks ( ).

The EAG requested alternative analysis where beginning a new therapy did not result in censoring/event (clarification A20), however this change had no effect on the results.

The EAG also requested information on the censoring rules (clarification A21). For EFS, of censoring events in the liso-cel arm were due to end of trial follow-up, and for the same reason in SOC arm. in both arms was censored at randomisation due to a lack of follow-up information.

2.2.8.2 Secondary Outcomes

2.2.8.2.1 Response Rates

People with unknown or missing response rates were classed as non-evaluable in this analysis. The company's description implies that responses to other antineoplastic therapies were included in this outcome if the subsequent therapy was started for reasons other than concerns over efficacy. It is unclear how many people had responses from subsequent therapies that were classed as responders. Aside from this potential issue, liso-cel achieved statistical significance for CRR at the time of the primary analysis (one-sided p<0.0001).

For liso-cel vs SOC, the CR rate was 68/92 vs 40/92 and the PR rate was [redacted]. These participants were included in the duration of response analysis which demonstrated a longer response for liso-cel ([redacted]), however this was not included in the formal hypothesis testing. The Kaplan-Meier plot for this analysis is shown in Figure 2, where loss of response can be seen to occur late in the follow-up for both arms. An analysis of the duration of only complete responses demonstrated a slightly larger difference ([redacted]).

Figure 2: Kaplan Meier plot of duration of response for all responders (taken from Figure 7 of Company Submission)

2.2.8.2.2 Progression-free survival

Whilst PFS is more commonly used than EFS, in this indication the company states the EFS is more relevant as treatments at this stage have curative intent, and so stable disease is not a successful outcome. The main difference between these outcomes is how people with stable disease were considered. Having stable disease beyond 9 weeks or beginning a new therapy due to loss of CR beyond 18 weeks did not count as an event in the PFS analysis.

For PFS, trial participants were censored if they received a new treatment, on the grounds that they would otherwise receive benefit from this subsequent treatment which would bias the comparison. The company states that the results remain biased as this censoring is informative as these censored patients are more likely to experience a later progression. The EAG accepts this could be an issue, however it is likely the magnitude of effect is small as the majority of EFS events were also disease progression events. People were also censored if they had no follow-up assessments, or did not experience a PFS event at the end of the trial follow-up.

Statistical significance was achieved for PFS in the primary data analysis, with one-sided p-value <0.0001.

As [redacted] censoring events on the SOC arm were due to beginning a new therapy, compared to [redacted] for liso-cel (clarification response Table 11), the EAG requested an alternative analysis where these people were not censored (clarification A20). As information on later disease progressions was available, the intention of the EAG was to capture a patients disease progression regardless of what therapies were received. However, the analysis performed by the company appears to directly replace these censoring events with a PFS event. As this appears to hold for every censored event visible on the Kaplan-Meier plot, the EAG is concerned over the validity of this analysis, and the possibility that PFS events have not been observed but instead has just been assumed to occur at the point of switching. The company's analysis is almost identical to the original EFS analysis, which is not what the EAG expected.

2.2.8.2.3 Progression-free survival on subsequent therapy (PFS2)

As described in the original CS, the desired PFS2 outcome is defined as “the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death from any cause.” The EAG interprets this to mean that a PFS2 event would be disease progression or death once a patient has switched treatments, regardless of whether they have already experienced a disease progression.

There was some confusion with this outcome as the TRANSFORM study originally defined as the “time from randomisation to second objective disease progression or death from any cause”, however this definition was less relevant for this appraisal. Some information provided by the company relates to this definition, rather than the one described in the CS.

The EAG focuses on the CS definition of PFS2, and notes it is perhaps the most important outcome, certainly for the cost-effectiveness modelling, as it includes the impact of subsequent therapies received, rather than this being a confounding effect. Given that participants receive potentially curative therapies at third line, it may be a better outcome from which to derive health states, rather than EFS. Despite this definition, the EAG remains uncertain over the analyses performed by the company relating to this outcome, as the information provided by the company suggests people in TRANSFORM could have multiple PFS2 events.

The company provided a Kaplan-Meier plot for this outcome (Clarification Response Figure 13) where a decreasing hazard rate can be seen, though no clear plateau is observed. The company did not provide an estimate of the hazard ratio and the plot did not contain censoring information, however the EAG was able to obtain a rough estimate of the unstratified hazard ratio by digitising the plot and fitting a Cox proportional hazards model which came out as [redacted]. Whilst this shows a benefit for liso-cel, the magnitude of the hazard ratio is different to the benefit estimated by the EFS outcome.

2.2.8.2.4 Overall survival

At the final data-cut, there were 34 death events in the liso-cel arm of TRANSFORM, and 42 death events in the SOC arm. The hazard ratio was not formally tested for significance at this stage, however the 95% confidence interval [redacted]. The company states that this is confounded by the crossover from SOC to liso-cel in the trial, potentially overestimating SOC OS and so underestimating the OS benefit of liso-cel. The EAG accepts this possibility however the impact may be small as CAR T therapy is permitted at 3rd line in NHS care. The difference in the trial was that CAR T was accessible more quickly meaning people may have been less ill when receiving it and slightly more people were well enough to receive CAR T. The EAG does not anticipate that the impact of this would sufficiently impact the hazard ratio to [redacted]. The Kaplan-Meier plot is shown in Figure 3, showing the potential for a small benefit for liso-cel, however the confidence intervals have not been included.

Figure 3: Kaplan Meier plot for overall survival from TRANSFORM (taken from Figure 9 of Company Submission)

The company performed analyses where the crossover effect was adjusted out by either the 2-stage or RPSFT approaches, however the EAG does not consider these relevant to this appraisal as subsequent CAR T therapy is routinely approved for NHS care.

2.2.8.3 Subgroups

The company conducted a series of subgroup analyses for the primary outcome (EFS). Across a range of patient characteristics, the stratified hazard ratio was generally consistent. For some minor subgroups (region=Japan, disease type=FL3B or THRBCL, age≥75), a benefit was not observed, however these may have occurred by chance and be explained by the very small sample size of the relevant subgroup. See Figure 19 of the company submission for more detail. The EAG requested results of bridging therapy subgroups, which were mentioned in the statistical analysis plan, but not included in the original submission. These were provided (clarification response A12), and the treatment effect appeared consistent.

2.2.8.4 HRQoL

The company used three questionnaires to capture quality of life information within the TRANSFORM study: EORTC QLQ-C30, FACT-Lym and EQ-5D-5L, see CS Section B.2.6.4.

Across each of these measures, the EAG notes that the completion rate for both arms for any evaluation point after baseline is below 50%. The baseline score completion rates are also low, and the EAG has major concerns over whether the whole patient experiences on either treatment arm are truly represented in the data. The EAG presents information on completion rates in Table 10.

Table 10: Number of responses for HRQoL outcomes in TRANSFORM at select evaluation points.

		Baseline Score	9 Weeks	18 Weeks	12 Months	24 Months	36 Months
EORTC QLQ C30 Global	Liso-cel (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SOC (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACT Lym	Liso-cel (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SOC (n=92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L	Liso-cel/SOC combined (n=184)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: the EAG obtained these values from the CSR Table 14.3.5.11.1.1 but notes that for later time points the CSR provided differing values for the number of responses.

The EAG understands that data were not collected after crossover and so people who crossed-over to liso-cel are effectively excluded from the analysis beyond this point.

Across the EORTC QLQ-C30 domains presented by the company (global, fatigue, pain, physical functioning, cognitive function; Company Submission Figures 10-14), there was no clear long-term difference between arms from those contributing information to the analyses.

For FACT-Lym lymphoma subscale, the limited data from TRANSFORM suggested a deterioration beyond the minimally important difference for SOC which did not occur for liso-cel.

For EQ-5D-5L, the company first presented pooled data from both arms of the trial, which showed a weak increasing trend in quality of life over time, however this may be attributable to attrition bias. A comparison of the two arms showed that SOC consistently had a higher quality of life, however this might be attributable to the likely imbalance of patient characteristics, rather than the intervention.

The EAG concludes that there is no evidence to suggest people who achieve a good response to either liso-cel or SOC have a different quality of life based on the

treatment they receive. There is no evidence from the trial on quality of life for later lines of therapy.

2.2.8.5 Overview of adverse events in TRANSFORM

Treatment emergent adverse events (TEAEs) were presented for the safety analysis set (SAS), which included all participants who had taken at least one dose of study treatment. Reporting was done against the actual treatment received. For the SOC arm (n=91), the SAS was patients who received any treatment (e.g. re-induction immunochemotherapy with or without HDCT or ASCT). For the liso-cel arm (n=92), this was patients who received any study treatment, including bridging therapy if needed, lymphodepleting CT, and liso-cel or non-conforming product.

The EAG notes that the FDA clinical review considered there was limited use in comparing toxicities between the two treatment arms in TRANSFORM. They noted two considerations: '*1) Significant heterogeneity in the standard therapy arm in terms of exposure, the toxicities reported for this arm do not reflect the intended treatment plan and are likely underrepresented 2) The two arms have fundamentally different treatment modalities that have distinct toxicity profile'.*[30] The EAG agrees with this view.

The following sections summarise TEAEs occurring in TRANSFORM. See section 2.5.3 for a summary of TEAEs occurring in other liso-cel studies.

2.2.8.6 Summary of TEAEs

An overview of TEAEs is presented in Table 11. At least one TEAE was experienced by 98.9% of the SOC arm and 100% of the liso-cel arm, and Grade 3/4 events were experienced by 89.0% and 92.4%, respectively.

Deaths occurring in the SOC arm are presented separately for those occurring prior to receiving crossover therapy (9.9%) and those occurring after cross-over (56.9%) (Table 12). There were 34 (37.0) deaths in the liso-cel arm. Causes of death by category is also presented in Table 12.

Table 11: Overall summary of TEAEs in TRANSFORM, SAS

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

AE: adverse event; SAS: safety analysis set; SAE: serious adverse event; SOC: standard of care; TEAE: treatment emergent adverse event; TESAE: treatment emergent serious adverse event.
Source: Reproduced from CS Tables 26.

Table 12: **Overall summary of deaths, SAS**

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

AE: adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 27.

2.2.8.7 Common TEAEs and Grade 3/4 AEs

The most frequent TEAEs of any grade and of Grade 3/4 are presented in Table 13. In the SOC arm, the most frequent events of any grade were thrombocytopenia (72.5%), anaemia (68.1%), nausea (58.2%), neutropenia (54.9%) and diarrhoea ([redacted]%). The most common Grade 3/4 events were thrombocytopenia (68.1%), anaemia (56.0%); neutropenia (51.6%) and febrile neutropenia ([redacted]%). In the liso-cel arm, the most frequent events of any grade were neutropenia (82.6%), anaemia (67.4%), thrombocytopenia (59.8%), nausea (53.3%) and CRS (48.9%); and the most frequent Grade 3/4 events were neutropenia (81.5%), anaemia (52.2%) and thrombocytopenia (50.0%).

Table 13: **Incidence of TEAEs occurring in ≥ 20% of patients in either treatment group, SAS**

TEAE	SOC (n=91) n (%)		Liso-cel (n=92) n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	66 (72.5)	62 (68.1)	55 (59.8)	46 (50.0)
Anaemia	62 (68.1)	51 (56.0)	62 (67.4)	48 (52.2)
Nausea	53 (58.2)	4 (4.4)	49 (53.3)	3 (3.3)
Neutropenia	50 (54.9)	47 (51.6)	76 (82.6)	75 (81.5)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	38 (41.8)	2 (2.2)	37 (40.2)	0 (0.0)
Decreased appetite	32 (35.2)	4 (4.4)	21 (22.8)	1 (1.1)
Vomiting	27 (29.7)	2 (2.2)	18 (19.6)	1 (1.1)
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	24 (26.4)	0 (0.0)	30 (32.6)	2 (2.2)
Pyrexia	23 (25.3)	0 (0.0)	28 (30.4)	0 (0.0)
Hypokalaemia	22 (24.2)	4 (4.4)	21 (22.8)	4 (4.3)
Hypomagnesaemia[a]	21 (23.1)	1 (1.1)	15 (16.3)	0
Headache	21 (23.1)	1 (1.1)	40 (43.5)	4 (4.3)
Dizziness	13 (14.3)	0 (0.0)	22 (23.9)	0 (0.0)
Lymphopenia	11 (12.1)	9 (9.9)	25 (27.2)	24 (26.1)

Insomnia	10 (11.0)	0 (0.0)	19 (20.7)	0 (0.0)
Hypotension	6 (6.6)	0 (0.0)	19 (20.7)	3 (3.3)
Cytokine release syndrome	0 (0.0)	0 (0.0)	45 (48.9)	1 (1.1)

TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 28. [a] From CSR.

2.2.8.8 Adverse events of special interest

Adverse events of special interest (AESI) are summarised in Table 14. The most common AESI events of any grade in the liso-cel arm were neurological toxicity ([redacted]), CRS (48.9%), and prolonged cytopenia (43.5%). The most common Grade ≥3 events in the liso-cel arm were prolonged cytopenia ([redacted]), severe infections ([redacted]), and neurological toxicity ([redacted]).

Further details of AESIs following liso-cel are presented in CS Table 30 for neurological toxicity immune effector cell-associated events (any: 10.9%; Grade 3/4: (4.3%); clear definitions for this and for neurological toxicity as reported in the above paragraph are not provided in the CS. CS Table 31 reports details of CRS, and details of any grade infections and infestations in both arms are provided in CS Table 32.

Table 14: **Incidence of AESIs in either treatment group, SAS**

AESI	SOC (n = 91) n (%)	Liso-cel (n = 92) n (%)
All AESIs	[redacted]	[redacted]
All Grade 3/4 AESIs	[redacted]	[redacted]
All AESIs related to any study drug	[redacted]	[redacted]
All serious AESIs	[redacted]	[redacted]
All serious AESIs related to any study drug	[redacted]	[redacted]
All AESIs leading to death	[redacted]	[redacted]
All AESIs leading to withdrawal of any study drug	[redacted]	[redacted]

All AESIs leading to dose interruption of any study drug	[redacted]		[redacted]	
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**
Neurological toxicity	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Cytokine release syndrome	0 (0.0)	0 (0.0)	45 (48.9)	1 (1.1)
Prolonged cytopenia	3 (3.3)	3 (3.3)[a]	40 (43.5)	40 (43.5)[a]
Severe infections	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]
Infusion Related Reaction (IRR)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Second Primary Malignancy	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Tumour Lysis Syndrome (TLS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]
Macrophage Activation Syndrome (MAS)	[redacted]	[redacted][a]	[redacted]	[redacted][a]

[a]Based on March 2022 DCO, as breakdown of Grade 3/4 AESIs were not reported in the final DCO (October 2023). There were no changes in any grade AESIs between March 2022 and October 2023 data cuts.
Abbreviations: TEAE: treatment emergent adverse event; SAS: safety analysis set; SOC: standard of care.
Source: Adapted from CS Table 29: the company confirmed in Clarification response A16 that the data in CS Table 29 are correct, and that text in section B.2.10.3 stating 'AESIs of Grade 3/4 occurred in [redacted] patients ([redacted]%) who received liso-cel and [redacted] patients (55.4%) who received SOC' incorrectly attributed these values to the opposite trial arms.

2.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

No indirect comparison was performed in this appraisal.

2.4 *Critique of the indirect comparison and/or multiple treatment comparison*

No indirect comparison was performed in this appraisal.

2.5 *Additional work on clinical effectiveness undertaken by the EAG*

2.5.1 EAG updated searches

The EAG information specialist conducted an SLR update to identify additional publications since the last CS SLR searches undertaken in February 2024. The search strategies are reported in 7.3 Appendix 3. The EAG update search focused on SCT-eligible R/R LBCL patients receiving 2L treatment. All records identified through electronic database searches were assessed against the CS eligibility criteria by two independent EAG reviewers. The EAG screened 456 articles against the clinical effectiveness eligibility criteria. Of these, 24 were identified for potential retrieval of full texts; however, after a consensus discussion, none were ultimately retrieved as only two articles were related to liso-cel and neither provided any new information of relevance to the appraisal.

2.5.2 Additional liso-cel studies

As stated in Section 2.1.1, of the original 124 studies included in the company SLR only one was considered as relevant to inform the clinical evidence for the appraisal.[26] The EAG checked the details of the remaining 123 studies and requested summary details of two observational studies of CAR T therapies in clarification A6. The two observational studies,[31, 32] provide insights into real-world clinical effectiveness and safety of 2L CAR T therapy for LBCL, but the data presented for liso-cel in these two conference abstracts were limited.

The observational study by Dahiya (2023)[31] was conducted across five US academic institutions and retrospectively analysed data from 112 LBCL leukapheresed patients who received commercial CAR T therapy (9 liso-cel) between April 2022 and April 2023. The key findings for ORR, remission, PFS and OS were not provided for the liso-cel participants, and the efficacy results are of limited value to the current appraisal (see Clarification response A6 for further details). No deaths related to CRS or ICANS were reported.

The observational study by Koff (2023)[32], used data from eight US academic centres for Lymphoma Epidemiology of Outcomes (LEO) Cohort study and the Consortium for Real World Evidence (CReWE). The cohort included 1523 patients with

relapsed/refractory LBCL, aged ≥ 18 years, receiving 2L systemic therapy from 2002 to 2022. Only 88 participants received CAR T therapies at second-line, many during clinical trials, and no data were presented by the type of CAR T therapy received. As such the results are of limited value to the current appraisal (summarised in Clarification response A6).

The EAG agrees with the company that there are no relevant liso-cel data to include from these conference abstracts.

2.5.3 Adverse events in the literature

The EAG searched for additional data on AEs associated with liso-cel, and presents a summary of findings here.

A recent systematic review (Yamshon 2024[33]) compared the incidence of CRS, immune effector cell associated neurotoxicity syndrome (ICANS), hematologic toxicity, and infections associated with FDA- approved CAR T products for NHL.

Four liso-cel studies were included (the EAG notes that Cohort 1 – Europe (n=27) of the TRANSCEND WORLD study[34] was not included):

- TRANSFORM interim analysis (Kamdar 2022[29]), n=90
- TRANSCEND (Abramson 2022[35]), n=269
- PILOT (Sehgal 2022[36]), n=61
- TRANSCEND WORLD Cohort 3 - Japan (Makita 2022[37]), n=10

The review also included six axicabtagene ciloleucel studies and five tisagenlecleucel studies, but these are not summarised here. Results for liso-cel and are summarised in Table 15.

There was little statistical heterogeneity between the liso-cel studies for any grade and Grade ≥3 CRS, indicating the incidence of events was similar between studies. There was moderate statistical heterogeneity for Grade ≥3 ICANS and Grade ≥3 Infection, and considerable statistical heterogeneity for the other events (Table 15), suggesting differences in incidence between studies. However, there was no clear pattern (e.g. whether events were lower or higher in TRANSFORM) and the clinical impact of this is unclear. In addition, the FDA clinical review considered the key

adverse events to be comparable across the three studies they considered[30] (see below).

Yamshon 2024[33] note a number of limitations to their analysis, such as differences across the trials in inclusion criteria, adverse event grading scales, and toxicity treatment practices. Results should therefore be viewed with caution.

Table 15: **Summary of results of pooled incidence rates of AESIs for liso-cel**

	Pooled incidence rate, % (95% CI) Heterogeneity, I^2
	Liso-cel 4 studies, n=430
CRS – any grade	43 (38, 49) I^2 = 8%
CRS - grade ≥3	1 (0.1, 0.3) I^2 = 0%
ICANS – any grade	22 (12, 34) I^2 = 79%
ICANS – grade ≥3	6 (3, 10) I^2 = 30%
Anaemia – any grade	3 studies, n not reported 49 (17, 63) I^2 = Not reported
Anaemia – grade ≥3	39 (17, 63) I^2 = 91%
Thrombocytopenia – any grade	3 studies, n=340 47 (12, 84) I^2 = 87%
Thrombocytopenia – grade ≥3	38 (19, 59) I^2 = 88%
Neutropenia – any grade	3 studies, n=340 64 (46, 81) I^2 = 70%
Neutropenia – grade ≥3	69 (50, 86) I^2 = 89%
Infection – any grade	1 study, n=10 10 (3, 45)
Infection – grade ≥3	11 (8, 14) I^2 =34%
Febrile neutropenia – any grade	3 studies, n=420 8 (2, 17) I^2 = 79%

Data from Yamshon 2024[33]

FDA clinical review

The FDA clinical review[30] pooled safety data from three liso-cel studies (n=418):

- TRANSFORM interim analysis (Kamdar 2022[29]), n=89
- TRANSCEND (Abramson 2022[35]), n=268
- PILOT (Sehgal 2022[36]), n=61

Non-fatal serious adverse events are summarised in Table 16, Grade ≥3 AEs occurring among the 418 pooled participants are presented in Table 17, and AESI are presented in Table 18. The FDA reviewer noted that key AEs were comparable across the three studies. The EAG noted some slight differences in the proportion of pooled adverse events between the FDA clinical review and the Yamshon 2024[33] systematic review, e.g. for CRS. It is unclear whether this is due to an error, recoding of adverse events in the FDA review, or some other reason.

Table 16: Non-fatal serious adverse events in liso-cel studies

System Organ Class and Preferred Term, n (%)	TRANSFORM N=89	PILOT N=61	TRANSCEND N=268	Total N= 418
Subjects with any serious TEAE	34 (38)	20 (33)	122 (46)	176 (42)
Blood and lymphatic system disorders	14 (16)	1 (2)	25 (9)	35 (8)
Febrile neutropenia	14 (16)	1 (2)	25 (9)	40 (10)
Immune system disorders	12 (14)	8 (13)	49 (18)	69 (17)
Cytokine release syndrome	12 (14)	8 (13)	49 (18)	69 (17)
Nervous system disorders	5 (6)	1 (2)	41 (15)	47 (11)
Encephalopathy	2 (2)	1 (2)	12 (5)	15 (4)
Aphasia	2 (2)	0	9 (3)	11 (3)
Tremor	1 (1)	0	3 (1)	4 (1)
Infections and infestations	14 (16)	5 (8)	28 (10)	47 (11)
Infections with pathogen unspecified	7 (8)	3 (5)	24 (9)	34 (8)
Bacterial infectious disorders	5 (6)	2 (3)	14 (5)	22 (5)
Viral infectious disorders	3 (3)	0	4 (2)	7 (2)
Fungal infectious disorders	0	0	3 (1)	3 (1)
Psychiatric disorders	0	3 (5)	20 (8)	23 (6)
Confusional state	0	3 (5)	8 (3)	11 (3)
Mental status changes	0	0	7 (3)_	7 (2)

Respiratory, thoracic and mediastinal disorders	2 (2)	2 (3)	12 (5)	16 (4)
Pulmonary embolism	2 (2)	2 (3)	1 (0.4)	5 (1)
Dyspnea	0	0	15 (6)	15 (4)

Source: FDA Clinical Review[30]

Table 17: **Grade ≥3 AEs in ≥2% of 418 participants (3 studies) with liso-cel**

Grade ≥3 AEs, n (%)	**Pooled studies n=418**
Infections - pathogen unspecified	65 (16)
Encephalopathy	45 (11)
Sepsis	27 (6)
Dyspnea	24 (6)
Hypertension	22 (5)
Pneumonia	21 (5)
Musculoskeletal pain	19 (5)
Hypotension	19 (5)
Bacterial infection	19 (5)
Fatigue	18 (4)
Cytokine release syndrome	16 (4)
Abdominal pain	16 (4)
Edema	15 (4)
Dizziness	15 (4)
Aphasia	14 (3)
Decreased appetite	13 (3)
Delirium	12 (3)
Urinary tract infection	11 (3)
Headache	10 (2)
Renal failure	10 (2)
Motor dysfunction	10 (2)
Cardiac Arrhythmias	9 (2)
Gastrointestinal haemorrhage	9 (2)
Nausea	8 (2)
Thrombosis	8 (2)
Hemophagocytic lymphohistiocytosis	7 (2)

Source: FDA Clinical Review[30]

Table 18: **AESI among 418 participants (3 studies) with liso-cel. pooled studies, n=418**

TEAEs	**Grade 1-5**	**Grade ≥3**
Subjects with any CRS	191 (46)	15 (3.5%)
CRS symptoms		

fever	183/191 (96)	11/191 (6)
hypotension	83/191 (43)	11/191 (6)
tachycardia	55/191 (29)	1/191 (1)
chills	44/191 (23)	0
hypoxia	32 (17)	14 (7)
Headache	24 (13)	5 (3)
Fatigue	24 (13)	1 (1)
Subjects with any neurologic toxicity (NT)	136 (33)	42 (10)
NT symptoms		
Encephalopathy	83 (20)	25 (6)
Tremor	45 (11)	1 (0)
Aphasia	30 (7)	9 (2)
Headache	24 (6)	5 (1)
Dizziness	22 (5)	2 (0)
Delirium	21 (5)	5 (1)
Ataxia	17 (4)	1 (0)
Neuropathy peripheral	4 (1)	0 (0)
Motor dysfunction	3 (1)	1 (0)
Paresis	3 (1)	2 (0)
Seizure	3 (1)	3 (1)
Infections	170 (41)	54 (13)
Bacterial infections	56 (13)	22 (5)
Infections – pathogen unspecified	82 (20)	34 (8)
Febrile neutropenia	40 (10)	40 (10)
Fungal infections	45 (11)	2 (0.5)
Viral infections	11 (3)	8 (2)
Prolonged cytopenias[a]	382 (91)	157 (38)
Neutropenia	373 (89)	94 (22)
Thrombocytopenia	172 (41)	127 (30)
Anemia	139 (33)	31 (7)
Hypogammaglobulinemia	62 (15)	1 (0)
Myelodysplastic syndrome	8 (2)	8 (2)

[a]not resolved by day 29 post lisocabtagene maraleucel infusion

TRANSCEND FL study

TRANSCEND FL[38] was a Phase 2 study (n=130) of liso-cel for R/R FL, including third line patients and second line with progression of disease within 24 months from first-line immunochemotherapy. Rates of any grade CRS were slightly higher in

TRANSCEND FL than in TRANSFORM, but rates of neutropenia, anaemia, thrombocytopaenia and prolonged cytopenia were lower in TRANSCEND FL.

Table 19: **Key AESI reported in TRANSCEND FL**

	2L+ FL, n=130	
TEAE, n (%)	**Any grade**	**Grade ≥3**
Neutropenia	85 (65)	76 (58)
Cytokine release syndrome	75 (58)	1 (1)
Neurological event [a]	20 (15)	3 (2)
Anaemia	49 (38)	13 (10)
Thrombocytopenia	33 (25)	13 (10)
Prolonged cytopenia [b]	-	29 (22)
Severe infections	-	7 (5)
Hypogammaglobulinemia	6 (5)	-
Second Primary Malignancy	4 (3)	-
Macrophage Activation Syndrome / hemophagocytic lymphohistiocytosis	1 (1)	-

[a] investigator identified neurological AEs related to liso-cel. [f] Defined as grade ≥3 laboratory abnormalities of neutropenia, anaemia or thrombocytopenia on day 29.

2.6 *Conclusions of the clinical effectiveness section*

The CS presents direct evidence from the TRANSFORM trial, an open-label Phase III multinational RCT comparing liso-cel with SOC in people with R/R LBCL who are eligible for ASCT.

A statistically significant improvement was found with liso-cel compared with SOC in the primary outcome EFS (HR [redacted]), and secondary outcomes CRR (RR [redacted]), ORR (RR [redacted]), PFS (HR [redacted]) and PFS2 (HR [redacted]). The HR for OS [redacted] (HR [redacted]). The most frequent Grade 3/4 events in the liso-cel arm were neutropenia (81.5%), anaemia (52.2%) and thrombocytopenia (50.0%); in the SOC arm they were thrombocytopenia (68.1%), anaemia (56.0%) and neutropenia (51.6%).

The population in the TRANSFORM trial and the company's decision problem is narrower than that defined by the NICE scope. The EAG considers TRANSORM to have a high risk of bias due to deviations from the intended interventions allowed by the trial design. A high proportion (66.3%) of participants in the SOC arm were

eligible to crossover to liso-cel as part of the trial design. Approaches to censoring of these data may have introduced bias into the analysis.

Alternative analyses requested by the EAG had no effect on the EFS results, however the EAG has concerns with the validity of additional analyses requested for PFS. The EAG considers that PFS2 may be a more appropriate outcome than EFS for deriving health states, and notes that the magnitude of the HR is different to the benefit estimated by the EFS outcome. HRQoL data were presented in the CS but the EAG notes that completion rates were low and that data were not collected after crossover. Overall, the EAG considers that there is no evidence to suggest a difference between treatments in the quality of life of people who achieve a good response.

Generalisability issues:

There are a number of generalisability issues that the EAG believe important to consider when applying the results of TRANSFORM to UK clinical practice. In general, the EAG clinical experts are of the opinion that the baseline characteristics of TRANSFORM are broadly representative of people with R/R LBCL seen in clinical practice in the UK. The EAG considers that the proportion of participants receiving bridging therapy is lower than in UK practice, discussed further in Section 3.2.8.1.2. The options for first line treatment in the UK has changed since TRANSFORM commenced with a greater number of people anticipated to receive Pola+R-CHP at first line since the 2023 NICE recommendation, whilst [redacted] participants received prior Pola+R-CHP in TRANSFORM. The EAG also notes that in the SOC arm of TRANSFORM the time from confirmation of eligibility for crossover to administration of liso-cel was much quicker than would occur in clinical practice. Additionally, there was very little drop-out between leukapheresis and infusion in the liso-cel arm, with advice to the EAG suggesting this is not reflective of practice in real world settings. Finally, the subsequent therapies received in TRANSFORM are not reflective of recently approved therapies or UK practice (discussed further in Section 3.2.8.3), including the likelihood of liso-cel arm receiving a second CAR T treatment, and proportions receiving CAR T following SOC.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

3.1.1 Search strategy

Searches for cost-effectiveness and health-related quality of life (HrQoL) evidence were carried out separately in April 2020 on an appropriate selection of bibliographic databases, conference websites and grey literature sources, including websites of relevant HTA organisations. The searches were updated and re-run 5 times, the latest search was in February 2024 (CS Appendix G.1.1 Search strategy Tables 26-36 and H.1.1.1 Tables 48-56). The searches were limited to 2003 onwards as the first trial for rituximab (standard of care in newly-diagnosed LBCL) was published in 2002. The EAG note that it was reasonable to limit the searches for this reason. A supplementary search was carried out with the inclusion of additional economic terms with no date limit (CS Appendix G 1.1. Table 37).

The database search strategies are appropriately comprehensive and well-constructed. The searches include database-specific indexing and free-text terms for the population/ condition (R/R DLBCL) combined with filters for costing, economic and HRQoL studies (CS Appendix G.1.1.1 Search strategy Tables 26-36 and Tables 48-56). Omitting terms related to the intervention/ treatment type increases the sensitivity of the searches. The reasonably sensitive and non-validated search filters developed by CADTH (Canadian Agency for Drugs and Technologies in Health),[39] the validated NHS EED Economic filter[40] and the validated balanced McMaster filter[41] for economic and costing studies were applied (CS Appendix G.1.1.1 Electronic database searches Tables 27-36). The sensitivity maximising validated search filter developed by Arber et al (2017)[42] for health state utility values (HSUVs) was applied to the search for health-related quality of life studies (CS Appendix H.1.1.1 Electronic database searches Tables 48-56).

The search terms used for the retrieval of grey literature and conference sources are provided but the numbers of retrieved and included results are not (CS Appendix G.1.1.2 Grey literature, conference and other website searches Tables 37 and 38

and H.1.1.2 Grey literature, conference and other website searches Tables 57 and 58). The full details of the reviews examined in the hand-searches are also not reported (CS Appendix G.1.2 Study selection). Only conference proceedings from 2016 onwards were searched and conference abstracts published prior to 2018 were sought via hand-searches (CS Appendix G.1.2.1 Eligibility criteria Table 39). A search of older conference proceedings may have identified additional trials that were never published, to counter publication bias (H.1.1.2 Grey literature, conference and other website searches Tables 57 and 58).
The EAG had no further concerns with the company's search.

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

3.2.1 NICE reference case checklist

Table 20: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. A 50-year time horizon was used. The EAG considers this long enough to reflect all differences in costs and outcomes.
Synthesis of evidence on health effects	Based on systematic review	Utility values were derived from the TRANSFORM trial and ZUMA-1 3L axi-cel trial, TA895 for relevant scenario analyses.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. EQ-5D data were used to derive health effects

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rates should be applied per cycle rather than annually. Weekly discount rates should be applied for the first 5 years of the model cycle. Afterwards, annual discount rates should be applied in line with the model structure.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company used a partitioned survival model with three health states:

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

The cost-effectiveness of liso-cel is based on the TRANSFORM trial. EFS is the primary end point of the trial, defined as the time from randomisation to progressive disease, failure to achieve CR or PR by 9 weeks or the start of new antineoplastic therapy due to efficacy concerns or death, whichever occurs first.

The EFS curve determined the proportion remaining alive and event free. The OS curve determines the proportion of patients alive regardless of event status and the post-event state was calculated as the difference between the OS and EFS state.

The EFS data is mature but median OS was not reached. Mixture cure models were fitted to the EFS and OS TRANSFORM trial using the final DCO (October 2023). Mixture cure models divide the population into two groups: those who are 'cured' and those who are not. The probability of 'cure' is estimated by parametric models. The proportion of patients who experience 'cure' are subject to SMR of 1.09 and age and gender matched general population mortality risk. Mortality risk for those who do not experience cure is defined as parametric curves fitted to the TRANSFORM data.

Parametric models fitted to the EFS curve predicted a cure rate ranging from [redacted]% to [redacted]% for liso-cel and [redacted] to [redacted]% for SOC. The company prefers the log-normal model for both liso-cel and SOC EFS extrapolation with a predicted EFS cure fraction of [redacted]% in the liso-cel arm and [redacted]% in the SOC arm.

Parametric curves fitted to the OS data predicted OS cure fraction ranging from 55.8% to 63.4% for liso-cel and 50.7% to 54.5% for SOC. Similar to the EFS, curve, the company prefers the log-normal model for extrapolation OS in both arms which predicted an OS cure fraction of 60.3% and 51% respectively. Parametric models were chosen based on considerations of visual fit, statistical fit using AIC and BIC criteria, plausibility of long-term extrapolations for combined cured and non-cured fractions, predicted cure fractions and plausibility of extrapolation for non-cured patients and plausibility of hazard functions.

TTNT data were used to determine the timepoint for initiating next treatment which were applied as a single one-off cost in the post-event health state. TTNT was defined as the time from randomisation to death or the start of new antineoplastic therapy whichever occurred first. Parametric curves were fitted to the TTNT KM data for each arm. Parametric models were chosen based on visual inspection of fit, plausibility of long-term extrapolations for combined cured and non-cured population, plausibility of extrapolation for non-cured population and statistical fit using AIC and BIC criteria.

Intervention costs include CAR T tariff costs, bridging therapy and drug acquisition costs. CAR T tariff costs were assumed to include pre-treatment (leukapheresis and

lymphodepleting chemotherapy), treatment (liso-cel drug administration costs) and post liso-cel infusion cost (resource use and AE management costs up to 100 days after infusion). Patients who discontinued treatment prior to liso-cel infusion were assumed to incur bridging therapy and leukapheresis costs. SOC cost include drug acquisition and administration costs associated with re-induction immune chemotherapy as well as HDCT and ASCT. After progression from the event-free state, patients in the liso-cel arm assumed to receive SCT, chemotherapy and radiotherapy at 3L+. Patients in the SOC arm are assumed to receive SCT, chemotherapy and CAR T at 3L. A detailed breakdown of the proportion of patients receiving each treatment is presented in subsequent sections. Resource use was estimated from NHS reference cost and estimates used in previous appraisals. All costs were inflated appropriately to reflect current prices.

Quality of life values were derived from the TRANSFORM trial using the EQ-5D-5L data cross-walked to the 3L using standard algorithm. Regression models were fitted with baseline utility and other co-variates as predictors. A summary of the model base-case assumptions and inputs is presented in CS Table 70.

In the opinion of the EAG, progression from EFS state to a post-event health state does not reflect an objective change in health status. For example, a patient with stable disease in the event free health state transitions to a post-event health state after 9 weeks without an underlying worsening of prognosis. Furthermore, it does not appropriately consider for the possibility of cure at 3L+ which may bias the ICER. Patients in the trial receive curative therapy, including CAR T for SOC at 3L+. The difference between the EFS and OS cure fraction in the SOC group ([redacted] vs 51%), suggests that a significant proportion of patients in the SOC group will be cured at 3L+. Hence, patients in the SOC group who experience cure at 3L+ do not receive the corresponding health benefits associated with cure as they remain in the post-event state.

For these reasons, the EAG requested an alternative end point be implemented in the economic model. The model was partitioned into a pre-PFS-2 health state (encompassing 2L and 3L treatment) and a post PFS-2 health state (i.e. fourth-line patients). This allows patients to receive treatment with curative intent in both 2L and 3L settings. Resource use was estimated based on the EFS health state occupancy, but health outcomes were based on the PFS-2 heath state. A detailed critique of the

treatment effectiveness and extrapolation is presented in Section 3.2.6. Whilst an EFS-based model was accepted in TA895, it is not clear whether any suitable alternatives were available for consideration.

3.2.3 Population

The population modelled was based on the TRANSFORM trial. Patient baseline characteristics used in the model were derived from the TRANSFORM trial as presented in Table 7 above. The EAG considers the population largely appropriate for decision making. The EAG considers the starting age of the population ([redacted]) to be younger than the expected age of a UK relevant population. The starting age of a similar appraisal, TA895, had a starting age of 57.2 based on the mean age of the population in ZUMA-7. Data provided by NHS England suggests that the mean age of people who have received 2L axi-cel since it entered the CDF is 59 years old (based on data analysed on 17th July 2024), and the EAG uses this value in its base case analysis.

3.2.4 Interventions and comparators

Patients in the intervention group were split into those who received liso-cel infusion (97.8%) and those who did not receive liso-cel infusion (2.2%). Infused patients were modelled to incur the full cost of liso-cel and non-infused patients were modelled to incur the cost of leukapheresis and bridging chemotherapy. Of the 90 infused patients, one patient received a non-conforming product infusion. Costs associated with CAR T acquisition for patients who received a non-conforming product were not accounted for, although administration costs were included in line with patients receiving liso-cel.

Patients in the comparator group were modelled to receive SOC which included re-induction immunochemotherapy (98.9%) followed by HDCT and ASCT (46.7%).

3.2.5 Perspective, time horizon and discounting

The perspective follows NICE methods guide recommendations. The time horizon is 50 years and costs, and health outcomes were discounted at a discount rate of 3.5% per annum. The EAG disagrees with the annual application of a discount rate during the weekly cycle period of the economic model used in the company base case and prefers a per cycle discount rate for this period instead.

3.2.6 Treatment effectiveness and extrapolation

To inform their partitioned survival model health states, the company extrapolate data from the EFS and OS outcomes from the TRANSFORM trial. A consequence of using the EFS outcome is that the post-event population is heterogeneous as some patients in this group will be cured at third line, whilst others will not. Hence, the EAG does not consider it appropriate to refer to this post-event group as a "health-state". This approach is highly likely to underestimate the total QALYs for SOC as it those cured at 3rd line are modelled to have a lower quality of life than those cured at 2nd line.

The EAG prefers to instead use the PFS2 outcome to inform the model health-states, which the company implemented in the model in response the EAG's request (clarification B3). Patients experiencing a PFS2 event are unlikely to be cured, whilst those without a PFS2 event are likely to be cured. The EAG considers that this division is more distinct and makes for better defined health-states.

All outcomes are extrapolated using mixture cure model versions of standard parametric models. The EAG accepts the rationale for using these models which assume a cure, as this is consistent with the intention and data for CAR T therapies, and has been used in other technology appraisals of similar technologies. The output from the mixture cure models fitted by the company report a cure-proportion, that is a proportion who are not at risk of the event. This can be helpful when distinguishing between different models, but relies on data being sufficiently mature to produce an accurate estimate of this proportion.

3.2.6.1 Event free survival

The company extrapolate EFS data from both arms of TRANSFORM. The company report that the assumption of proportional hazard rates between arms did not hold and so extrapolated each arm separately using a set of candidate mixture cure models. The model does not apply background mortality to EFS meaning the EFS extrapolations eventually cross the OS extrapolations.

For liso-cel, the company rule out generalised gamma and Gompertz models based on their interpretation of clinical expert input from TA895, where it was noted that relapses were likely to occur within the first two years. As these models predicted that over 10% of the non-cured population would still be event-free at 2 years, the company deemed these models implausible. The EAG is not clear how the company has arrived at the 10% threshold it has applied, and does not consider this strong justification for ruling out these models. The EAG notes that these two models produce the most pessimistic predictions for EFS of liso-cel, whilst all other models produce almost identical predictions (Figure 29 of Company Submission).

From the remaining models, the company opted for the log-normal model based on its goodness of fit statistics.

Whilst the EAG does not support using EFS outcome in the economic modelling, it has a preference for the generalised gamma model, as this has the best statistical goodness of fit, and produces a cure fraction that is most consistent with long-term follow-up for axi-cel in ZUMA 7, which has an EFS rate of 39% at 4 years.[43]

For SOC, the company notes the all the models produced very similar predictions (Figure 33 of Company Submission). The company select the log-normal model as it was consistent with their preferred extrapolation for liso-cel and was the model with the second-best goodness-of-fit statistics. The company also considers the generalised gamma as plausible as it had the best goodness-of-fit statistics. The EAG prefers the generalised gamma distribution, for consistency with its preferred extrapolation for EFS of liso-cel, but accept the log-normal model as plausible.

3.2.6.2 Progression free survival on second therapy (PFS2)

As stated earlier, the preference of the EAG is to instead use the PFS2 outcome to inform the model health states. Information on the extrapolation of this outcome was provided in the company clarification responses (B3 and Appendix B).

Whilst the company prefer not to use this approach, they still present their preferred set of models for this outcome for liso-cel and SOC. A limitation of the information provided was that it omitted details on censoring and the number of people at risk. The EAG considers that there is still considerable uncertainty over the cure rates for this outcome, and hence also for overall survival.

As with EFS, the company model does not apply background mortality of PFS2, meaning it will converge with the OS extrapolation at some point.

For liso-cel, following a similar algorithm to selecting a preferred model to EFS, the company select a log-logistic model, which estimates a cure fraction of [redacted]. The EAG accepts the company's choice as plausible, however the EAG prefers to use the Weibull model as the associated cure rate ([redacted]%) is most consistent with the 5 year overall survival rate observed in ZUMA-7 (~52%).[43] The EAG expect the PFS2 and OS extrapolations would converge between 5-10 years, with minimal or no occupancy of the post-PFS2 health state beyond this point as people are unlikely to be alive if they have not been cured. The Weibull does have slightly inferior goodness-of-fit statistics, however the differences are not considered important.

For SOC, the company rule out the generalised gamma and exponential model based on their implausible predictions for non-cured patients. From the remaining models, the company selects the log-normal model based on goodness-of-fit statistics.

The EAG compares the model predictions to long-term follow-up from ZUMA-1, where axi-cel is used in 3rd line setting.[44] Whilst not all patients will receive CAR T at 3rd line, the EAG anticipates that most will receive it as it has a positive recommendation from NICE. The EAG's clinical experts advised that ~10-20% of patients may instead receive palliative care. Whilst the true cure proportion for this population is unknown, the EAG considers both the log-normal and the log-logistics models as plausible, as their cure rates ([redacted]) are consistent with the 5 year OS rate reported from ZUMA-1 of 42.6%, which when scaled down to apply to the

80-90% of the population comes gives a range of (34.08%, 38.34%). The EAG select the log-logistic model for their base-case analysis.

3.2.6.3 Overall survival

For this outcome, again the company extrapolate data from both arms of TRANSFORM. Mixture cure models are fitted separately to each arm, and no assumption of proportionality is made. The company assessed whether such an assumption was appropriate and found it was not violated, however the company still opted for independent modelling of both arms for consistency with their EFS modelling. For all patients considered cured, the company apply a standardised mortality ratio of 1.09 to general population background mortality, which is obtained by Maurer et al. (2014) and is consistent with other similar appraisals. The EAG is content with this approach to modelling.[45]

The EAG considers the OS data less mature than the EFS and PFS2, as fewer events have been observed, and it is less likely that the true cure proportion is being estimated accurately. This is support by simulation studies by Kearns *et al*. and Grant *et al*. who showed that cure models fitted to short follow-up consistently overestimated the cure proportion.[46, 47] The EAG also notes that the OS follow-up from TRANSFORM is less mature than that of ZUMA-7, in addition to the much smaller sample size of TRANSFORM. Hence the EAG considers ZUMA-7 a more reliable for source for estimating long-term efficacy.

For both arms of TRANSFORM, the company consider the visual fit, the plausibility of extrapolations, the predicted survival of non-cured patients, the cure proportion and goodness of fit statistics.

For liso-cel, the company opt for the log-normal mixture cure model, having ruled out the exponential and Gompertz for poor visual fit, and ruling out the Weibull and Gamma due to their low prediction of 4 year survival for non-cured patients. Of the remaining extrapolations, the log-normal was the model that produced a cure-fraction (60.3) closest to predictions made by their clinical experts. The company report in their text that the range of the most plausible cure proportions predicted by their experts was [redacted], however Table 40 of the company submission shows the

mean values of the lower and upper plausible values were [redacted] respectively.

The EAG considers the company's preferred model to be too optimistic, as the OS cure rate is much higher than is predicted by the models fitted to PFS2 data. The EAG anticipates the PFS2 outcome to be highly predictive of OS and has the benefit of observing more events than OS within the current follow-up. The EAG is not aware of justification to support such a large difference based on the company's preferred models for each outcome (60.3% vs [redacted])

The EAG also compared extrapolations from this appraisal to predictions for axi-cel (TA895), another CAR T therapy. A key difference between TA895 and this current appraisal is that 3rd line CAR T (axi-cel) is now recommended, whereas it was previously only available through the CDF and so it was not accounted for in the economic modelling for the SOC arm in TA895. However, the CAR T arms are unaffected by this change and so the data and assumptions are more generalisable across the treatments and trials. The EAG notes that in TA895, a generalised gamma and log-logistic extrapolation were both considered plausible by the committee. Whilst the exact cure proportions from these models are not publicly available, the EAG estimates these to fall between 40% and 50% from visual inspection of the extrapolations (Figure 4).

The EAG compares observed and predicted time-to-event outcomes from follow-up of 2L axi-cel and liso-cel (Table 21). The EAG notes that across outcomes, that liso-cel shows short term benefit compared to axi-cel, however the benefit appears to reduce as follow-up increases. This could be attributed to the more favourable safety profile of liso-cel compared to axi-cel, and the EAG do not consider the evidence strong enough to support a long-term benefit. The EAG sought to compare the duration of response outcome across trials, to inform on potential differences in long-term efficacy, however this was not possible as median follow-up was 33.9 months in TRANSFORM and the median DOR was not observed, whilst median DOR in ZUMA-1 was 41.7 months.[43]

Even the most pessimistic extrapolation of OS from TRANSFORM (exponential) predicts a higher long-term survival rate than what was accepted in TA895.

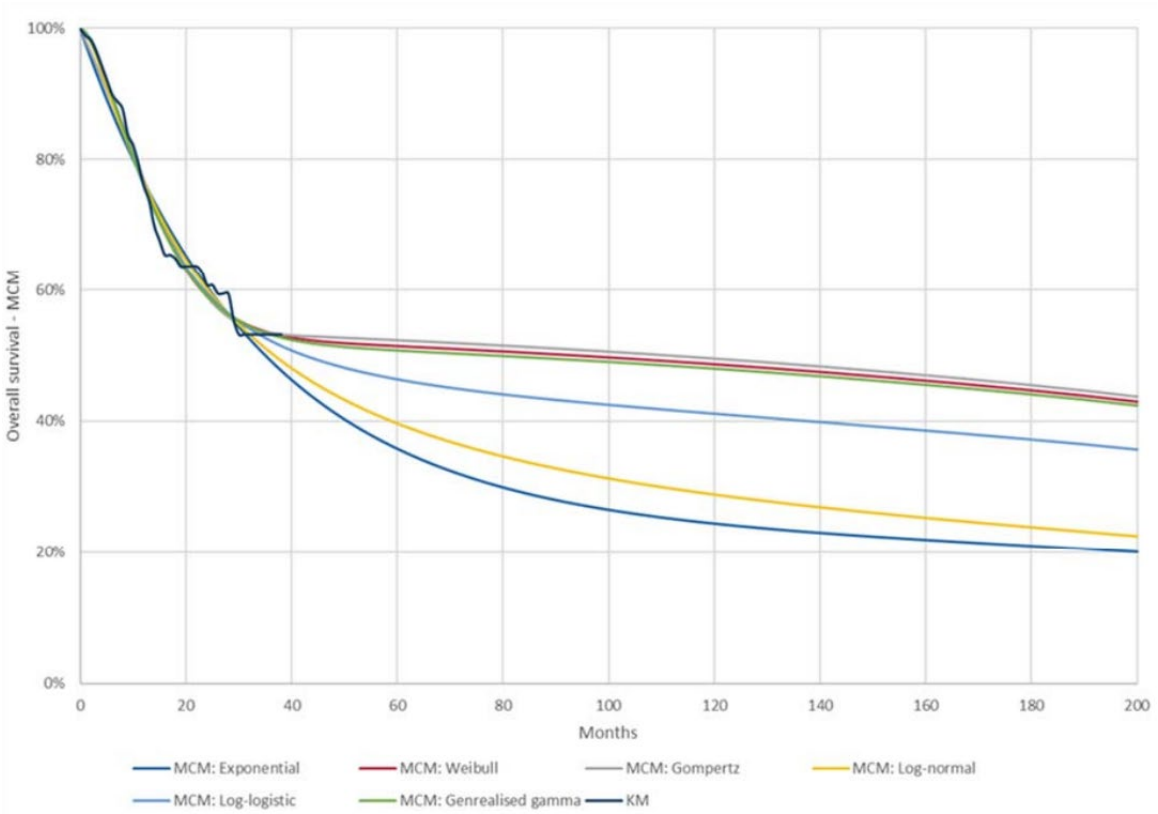

Figure 4: Extrapolations of axi-cel taken from EAG Report of TA895, Figure 9.

Table 21: Comparison of overall survival related outcomes and predictions for liso-cel and axi-cel

	Axi-cel (ZUMA 7)	Liso-cel (TRANSFORM)	Difference
EFS:			
1 year	49%	[redacted]	[redacted]
2 year	44%		
3 year	41%	45.8%	4.8%
4 year	39%	N/A	-
OS:			
1 year	76%	83.5%	7.5%
2 year	60%	67.5%	7.5%
3 year	56%	62.8%	6.8%
4 year	55%	N/A	-
PFS:			
1 year	52%	63.0%	11.0%
2 year	46%	57.0%	11.0%
3 year	44%	50.9%	6.9%
4 year	41%	N/A	-
Predicted OS:	GenGam / Log-log	Log-norm / Exponential	
5 year	50.5% / 46.2%*	59.4% / 57.5%	-
10 year	47.7% / 41.1%*	54.0% / 50.2%	-
15 year	43.8% / 37.0%*	48.5% / 44.8%	-

*Estimated from EAG digitization from TA895 committee papers.

The EAG identified a real-world study which compared outcomes for people who received liso-cel or axi-cel.[48] This abstract by Portuguese *et al*. did not show any clear OS benefit for liso-cel (Figure 5). In addition, two published indirect comparisons comparing 3L axi-cel and liso-cel found that axi-cel was associated with a significant OS benefit (HR = 0.53, 95% CI = 0.34-0.82; HR = 0.54, 95% CI = 0.37, 0.79).[49, 50]

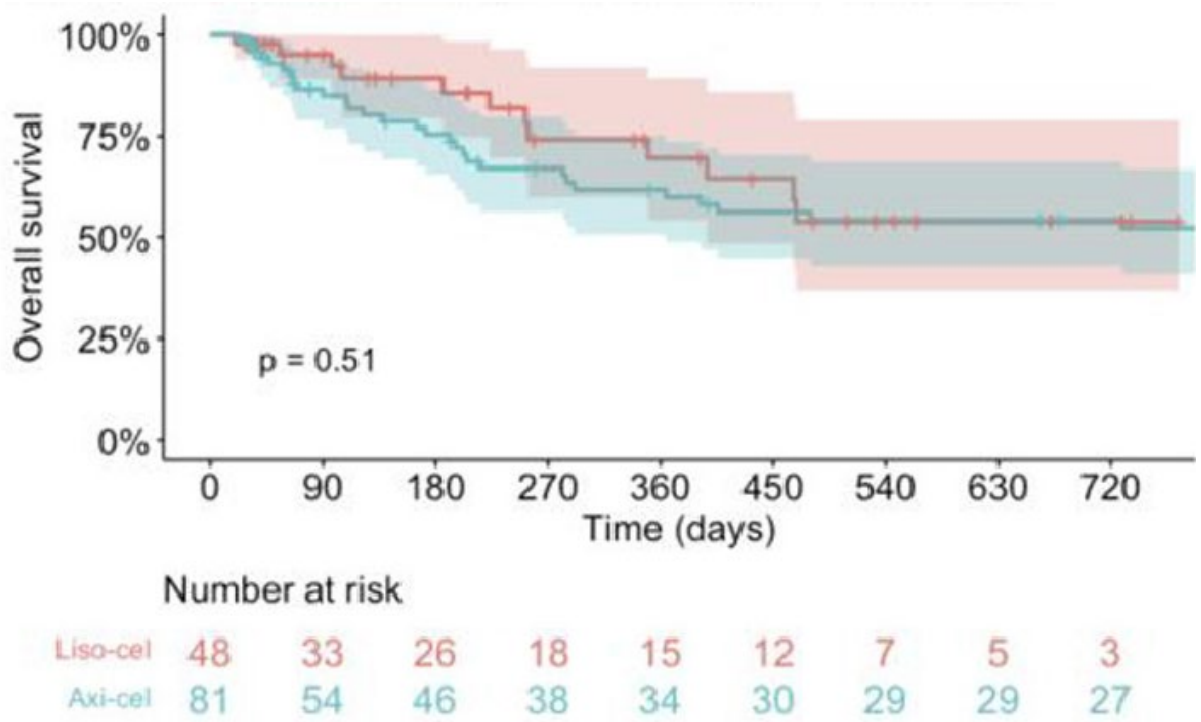

Figure 5: Real world overall survival of liso-cel and axi-cel (taken from Figure 2 of Portuguese et al.)

The results of the company's preferred selection of models for liso-cel EFS and OS are shown in Figure 6. The company assumptions show a crossing of EFS and OS curves for liso-cel from roughly 18 years. Beyond this point, there are no people remaining the post-EFS event health state. The EAG finds this implausible as there is a potential for curative ASCT being received at third line for a small number of people.

[redacted]

Figure 6: EFS and OS curves from company's preferred modelling for liso-cel.

For these reasons, the EAG conclude that the large OS benefit modelled for liso-cel by the company to be implausible and inconsistent with currently available information.

Instead, the EAG uses SurvInt, a freely available tool which can be used when standard modelling approaches fail to provide a plausible extrapolation.[51] The EAG aimed to obtain a model that is consistent with the early follow-up from TRANSFORM, the long-term follow-up of ZUMA-7 and also the cure rate for PFS2. The inputs for SurvInt were as follows:

[t1, S(t1)] = [11.05,0.85] - taken from TRANSFORM

[t2, S(t2)] = [48.00, 0.55] - taken from 4-year follow-up from ZUMA-7

Cure proportion = 0.50 - estimated for consistency with cure proportions of PFS2 and extrapolations from ZUMA-7

The EAG selected a log-logistic model as this was the most visually consistent with the TRANSFORM data. This model is also consistent with the company's rule for selecting a model which predicts <10% of non-cured people are alive at 4 years (9.97%).

A visual representation of the EAG's preferred log-logistic model using SurvInt is shown in Figure 7, compared to digitised TRANSFORM data. It deviates from the TRANSFORM data when in the tail when there is a high rate of censoring, and is instead consistent with the ZUMA-7 observed data (not shown).

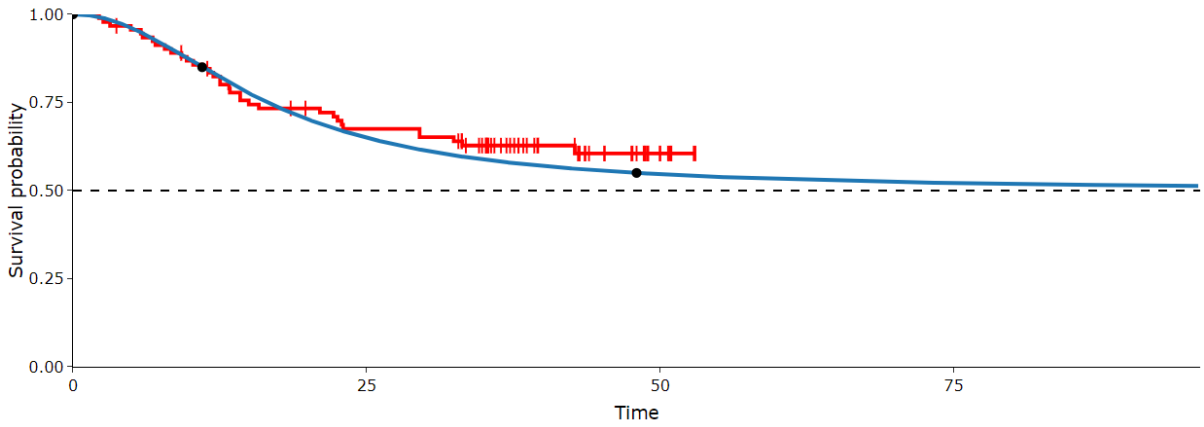

Figure 7: EAG preferred log-logistic extrapolation for liso-cel obtained using SurvInt

The resulting Markov Trace for the EAG's preferred assumptions is shown in Figure 8. The population of the post-PFS2 event remains small and is zero beyond roughly 6 years.

Figure 8: PFS2 and OS curves for liso-cel from EAG preferred assumptions

For SOC, the company select a log-normal model based on statistical goodness-of-fit, despite acknowledging that all candidate models likely overestimated long-term survival. The cure proportions ranged from 50-55% which were outside the range predicted by their clinical experts (%) The EAG agrees that due to the immaturity of the data, it is likely that the cure proportion is overestimated by all models.

The combined company assumptions for EFS and OS result in the modelling that there are no people remaining in the post-EFS-event health-state beyond 30 years (Figure 9). The EAG considers this implausible, as there are likely to be some individuals cured by 3rd line CAR T in this group.

Figure 9: EFS and OS curves from company's preferred modelling for SOC.

The company conducted a scenario analysis where they fitted models separately to the SOC arm of TRANSFORM and to the CORAL study, which included patients using SOC without the influence of 3L CAR T therapy. They then combined these models using a 66.25% weight for the TRANSFORM extrapolation, and 33.75% weight for the CORAL extrapolation, however it is not clear how these percentages were obtained and they do not seem to account for the proportion of the TRANSFORM SOC population who did not receive subsequent CAR T. Hence, the EAG does not consider the methodology of this approach robust.

In the absence of alternative options, the EAG preference is to use SurvInt to obtain a plausible extrapolation for SOC. As the SOC arm from ZUMA-7 was not a suitable reference, all inputs to SurvInt came from TRANSFORM:

[t1, S(t1)] = [6.59,0.86] - taken from TRANSFORM

[t2, S(t2)] = [17.76, 0.63] - taken from TRANSFORM

Cure proportion = 0.35 - estimated for consistency with cure proportions of PFS2

Whilst this model underestimates the tail of the Kaplan-Meier curve from TRANSFORM, the EAG considers this may be an appropriate deviation given the faster access to 3L CAR T that occurred in the trial compared with real world practice and the other differences between 3L+ treatments received in TRANSFORM compared with real-world NHS care (section 3.2.8.3). Whilst the percentage of uncured patients remaining alive at 4 years is just above the company's 10%

threshold, the EAG considers that a difference here between arms may be reflective of the potential greater efficacy of 3L+ therapies in a CAR T naïve population as hypothesized by their clinical experts, but also that the company's threshold is somewhat arbitrary.

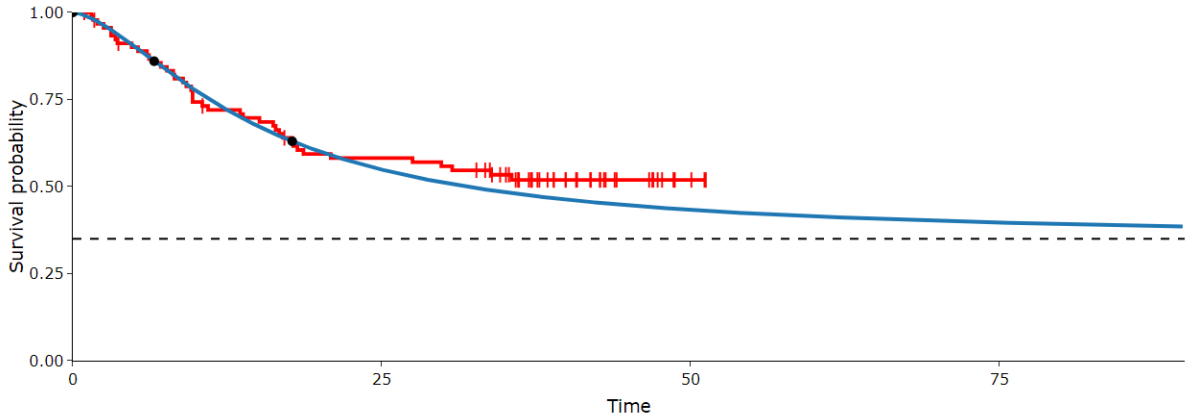

Figure 10: EAG preferred log-logistic extrapolation for SOC obtained using SurvInt

The EAG's preferred curves resulting Markov trace can be seen in Figure 11. The PFS2 and OS curves cross at roughly 6 years, beyond which the post-PFS2 event health state is zero.

Figure 11: PFS2 and OS curves for SOC from EAG preferred assumptions

3.2.6.4 Time to next treatment

The company extrapolate time-to-next treatment data from the TRANSFORM trial to inform the modelling of subsequent treatments.

A TTNT event included death or starting a subsequent treatment. Hence, after estimating the TTNT curve, the company then apply a multiplier, scaling down the incidences of beginning new treatment, based on the proportion of new-treatment events out of all TTNT events.

At 5 years, the company assumed that no new TTNT events would occur related to the primary disease, and did not capture any subsequent treatment costs beyond this point.

For liso-cel, the company select a log-normal extrapolation, as this has the best AIC and BIC after excluding the generalised gamma model as it predicted >10% of non-cured patients to have not had a TTNT event at 2 years.

The EAG is unclear why there is disagreement between the EFS and TTNT liso-cel outcomes, with the TTNT extrapolations more optimistic, in particular given their similarity in descriptions. Whilst censoring information on TTNT is not provided, the EAG considers that the EFS outcome will be more mature, and likely to give a more reliable long-term extrapolation. EFS is also provided with information on censoring to support a more informed choice over the plausibility of the cure proportion. The EAG also note that the TTNT extrapolations are more optimistic than those published in TA895.

The EAG prefers to use the generalised gamma EFS extrapolation from TRANSFORM to model TTNT. This model is consistent with the EAG preferred OS extrapolation, allowing for some people to be cured by subsequent ASCT, and is also consistent with the TTNT rate from the TA895.

Table 22: Comparison of 5 year rates for TTNT-free for CAR T therapy.

	5 year TTNT liso-cel	5 year EFS liso-cel	5 year range from TA895 CAR T
Exponential	[redacted]	[redacted]	40.6% - 43.0%
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Gen Gamma			
Gamma			

For SOC, the candidate extrapolations of TTNT from TRANSFORM showed strong similarity. The company opted for the log-normal model for consistency with their choice of model for liso-cel and on statistical goodness-of-fit. The EAG prefer again to use an EFS extrapolation to inform TTNT, and opt for the log-normal model as it was an acceptable EFS model, and produces a 5 year estimate similar to what was modelled for SOC in TA895.

Table 23: Comparison of 5 year rates for TTNT-free for SOC.

	5 year TTNT SOC	5 year EFS SOC	5 year range from TA895 SOC
Exponential	[redacted]	[redacted]	19.7% - 20.7%
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Gen Gamma			
Gamma			

3.2.7 Health related quality of life

EQ-5D-5L was collected in the TRANSFORM trial. Out of the 184 patients in TRANSFORM, [redacted] were included in the EQ-5D analysis set. EQ-5D-5L data were mapped to the 3L using mapping function developed by Hernandez *et al*.[52]

A regression model was fit to the data adjusting for baseline utility (centred at the mean value of the EQ-5D evaluable population), liso-cel pretreatment, EFS status and grade 3 AE. Treatment independent utility values were used in the CEM for event-free and post-event health state.

AE disutility was estimated using multi-variate model adjusted for EFS events, Grade ≥ AEs, and lymphodepleting chemotherapy. Utility decrement derived from TRANSFORM were applied to all Grade ≥3 AEs and hypogammaglobulinemia for the average AE duration in TRANSFORM ([redacted]). Disutilities for CRS and neurotoxicity were derived from TA895. Lymphodepleting chemotherapy was associated with a disutility of [redacted] and applied for 3 days based on TRANSFORM data. Table 25 summarises the disutility estimate used in the model and the duration the AE were applied.

Patients who remain progression and event-free after 5 years are assumed to revert to general population utility levels.

Table 24: Summary of Grade ≥3 AE disutilities included in the economic model

AE	Utility decrement (SE)	Utility decrement source	Duration of AE (days)	Duration source
CRS	0.852	As per approach in TA895[53]	8.3	TA895[53]
Neurotoxicity	0.150	TA895[53]	40	TA895[53]
Hypogammaglobulinemia	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H [54]	[redacted]	TRANSFORM EQ-5D analysis (final DCO; October 2023); Multivariate Model H[54]
Neutropenia				
Thrombocytopenia				
Anaemia				
Lymphopenia				
Febrile neutropenia				
Hypophosphatemia				
Leukopenia				
Prolonged cytopenia				
Infections				
Hypertension				

The company implanted a scenario where PFS-2 were used rather than EFS. Utility for the post-PFS-2 health state were obtained from TA895, which used data from ZUMA-1. Table 25 summarises the utility values used for the PFS-2 state, EFS, post-event and post-progression health state.

Table 25 Summary of health-state utility values used in the base case economic analysis and PFS-2 scenario analysis

Health state	Utility (Mean)	Source
Event-free	0.852*	TRANSFORM EQ-5D analysis (final DCO; October 2023)
Long-term remission	0.853*	
Post-event	0.808*	
Pre PFS-2 event	0.852	TRANSFORM UK Utility analysis, 23 Oct 2023 DCO
Post PFS-2	0.72	Post progression utility value TA895, ZUMA-1 3L axi-cel
Long-term remission	0.853	TA895 final utilities (EFS: ZUMA-7, PD: 3L axi-cel trial)

*used in company base case

The EAG considers that utility and AE disutility were applied appropriately. However, the utility for the overall population who remain event-free and progression-free is too optimistic. The estimate used for event and progression-free population differs significantly from estimates used in previous appraisals. For example, in TA985, the committee accepted a utility value of 0.785 for patients who remain event-free at 2L. Indeed, the estimate used in the company base case is similar to general population utility levels (0.852 used in the company base case compared to general population utility estimate of 0.853; disutility of -0.001).

The EAG prefers a utility value of 0.785 for the overall population who are progression-free and event-free for the period where patients may be unwell and face uncertainty over their prognosis. After 5 years, the proportion of cohort who remain free of an event revert to general population utility levels. This approach is similar to the approach taken in TA895 and appropriately applies a significant utility benefit for the population cohort who are cured.

3.2.8 Resources and costs

Intervention and comparator costs were applied separately for each arm. Costs were considered from an NHS and PSS perspective. Resource use and costs are summarised across the following sections.

3.2.8.1 Intervention costs

The main costs associated with liso-cel consist of the CAR T tariff, bridging therapy costs and liso-cel drug acquisition costs. In this document, the EAG used costs as provided by the company. Prices used in the confidential appendix can be found in appendix 4 of this report.

3.2.8.1.1 CAR T tariff costs

CAR T tariff costs were assumed to include all costs associated with a decision to have CAR T until 100 days after infusion. The CAR T tariff costs include the following categories:

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

The CAR T tariff costs notably cover the cost of all treatment-related AEs except for treatment of hypogammaglobulinemia. A single CAR T tariff cost of £41,101 was applied in line with NICE TA895. The company commented that this likely overestimates the costs associated with liso-cel as they were calculated based on axi-cel which is associated with more CAR T related AEs. The EAG accept this point however is unable to comment on the magnitude of the impact as the breakdown of the calculation is not reported.

For patients who discontinued treatment prior to receiving lymphodepleting chemotherapy, they were assumed to incur costs of leukapheresis and bridging therapy only. Patients who received non-conforming product were assumed to incur CAR T tariff costs and administration costs. Drug acquisition costs were not applied.

The patient flow during CAR T pre-treatment period is summarised in Table 26.

Table 26 Patient flow during liso-cel pre-treatment period

	Liso-cel (TRANSFORM final DCO; October 2023)
Patients who undergo leukapheresis but do not receive CAR T infusion	2.17%
Patients who die prior to CAR T infusion	0.00%
Patients who receive planned treatment	96.74%
Patients who receive an out-of-specification CAR T product	1.09%
Total	100%

3.2.8.1.2 Bridging therapy costs

Bridging therapies were aligned with the TRANSFORM trial and included R-GDP, R-DHAP and R-ICE. The proportion of patients receiving bridging therapy was in the company base case was based on the TRANSFORM trial where 63% of patients received bridging therapy. Bridging radiotherapy was not included in the company base case but were considered in a scenario analysis alongside other novel therapies not included in the company base case based on clinical expert estimates. Bridging therapy costs were applied to patients receiving 3L CAR T therapy and assumed equivalent to the proportion of participants receiving liso-cel. Bridging therapy drug acquisition costs and the proportion receiving each regimen are outlined in CS Table 54.

Administration costs were applied to bridging therapy excluding oral therapies. The administration of R-DHAP included the cost of two days of inpatient administration while the administration of R-ICE included the cost of three days of inpatient administration. A maximum of one administration cost was applied per day for inpatient treatments. Administration costs applied in the model are detailed in CS Table 55.

The EAG has concerns regarding the costs applied in the company base case. The company base case assumes equivalence between the proportion and distribution of patients who received bridging therapy at 2L prior to liso-cel infusion with those in the SOC group who receive 3L CAR T. However, the bridging therapy used prior to liso-cel infusion at 2L (R-GDP, R-DHAP and R-ICE) were re-induction chemotherapies given to 2L SOC. Using the same bridging therapy at 3L CAR T does not consider the possibility that patients unresponsive to chemotherapy at 2L may are given the same therapy as bridging therapy at 3L. Unlike UK clinical

practice, bridging therapy distinct to the regimens received as part of the SOC intervention was not given to participants in the SOC group. Clinical experts consulted by the EAG suggested that the proportion of patients receiving bridging therapies and the distribution of bridging therapies will differ from those currently modelled in the company base case. In a study of CAR T use in the UK, Boyle *et al*. reported that 11% of CAR T patients received no bridging therapy or steroids.[55] Hence the EAG prefers to model that 89% patients receiving CAR T therapy will require bridging therapy rather than 63% in the company base case. The EAG also prefers to use the distribution of bridging therapies taken from Boyle *et al.*[55] Table 27 compares the preferred assumptions relating to bridging therapy by the company and EAG.

Table 27: Comparison of assumptions relating to bridging therapy associated with CAR T

	Proportion Receiving Bridging Therapy	R GDP	R DHAP	R ICE	PolaBR	Radiotherapy
Company Bridging Assumptions	63.04%	[redacted]	[redacted]	[redacted]	0.00%	0.00%
EAG Bridging Assumptions	89.00%	6.74%	6.74%	6.74%	64.04%	35.96%

3.2.8.1.3 Liso-cel acquisition costs

Liso-cel is administered as a single infusion with a list price of £297,000. A single PAS discount of [redacted] is applied to the list price of liso-cel and a cost of [redacted] applied in all analyses.

3.2.8.2 SOC costs

SOC costs were based on drug acquisition and administration costs associated with re-induction chemotherapy, HDCT and ASCT. 1/92 patients who did not receive SOC were assumed to not incur SOC acquisition costs but received subsequent therapy costs in the SOC arm.

3.2.8.2.1 Reinduction chemotherapy

Patients were modelled to receive R-GDP, R-DHAP and R-ICE as re-induction chemotherapies, in line with the TRANSFORM trial (final DCO; October 2023). All chemotherapy regimens were assumed to be delivered in in-patient settings except R-GDP. CS Table 56 presents a breakdown of costs associated with chemotherapy.

3.2.8.2.2 HDCT and ASCT

43/92 patients (46.7%) received HDCT and ASCT following immunochemotherapy. HDCT was assumed to include BEAM regimen. Administrative costs of BEAM were assumed to be included in the costs of ASCT. The drug acquisition and administrative costs of BEAM and ASCT are presented in CS Tables 56 and 57.

3.2.8.3 Subsequent treatment costs

Costs associated with subsequent treatment were applied as a one-off cost based on TTNT data from TRANSFORM trial. The company calculated what proportion of TTNT events were the initiation of new therapy, as opposed to death, and applied this to the TTNT extrapolation. For more information see CS Table 58. The resulting assumption was that 69.6% of liso-cel patients and 94.2% of SOC patients experiencing a TTNT event would receive a subsequent therapy. The EAG's clinical experts did not consider the SOC rate to be plausible of clinical practice and is inflated due to the design of the trial. They estimated that in practice roughly a third of patients would move to palliative care following an unsuccessful attempt at 2L ASCT. Hence the EAG modelled that 66% of SOC patients experiencing a TTNT event would receive subsequent therapy, which is plausibly similar but slightly lower than what was modelled for liso-cel, which the EAG did not change.

The distribution of subsequent therapies applied the company came from TRANSFORM. The EAG compares this to estimates from the company's clinical experts in Table 28. The EAGs clinical experts suggested values consistent with the company's experts' estimates, and so the EAG opt to use these estimates in their base case.

For 3L+ chemotherapy, patients were assumed to receive 100% R-Bendamustine in an outpatient setting. Only drug acquisition costs and administration costs were considered at 3L+. AE costs were not considered.

Patients receiving CAR T therapy at 3L+ were assumed to incur CAR T tariff costs, bridging therapy costs and drug acquisition costs of axi-cel (at list price: £280,451)

The EAG considers the subsequent treatment distribution of novel therapies used in TRANSFORM and thus the company base case not reflective of UK practice. Based on data received from NHS England, the EAG prefers to use estimates from the clinical experts consulted by the company for both subsequent therapy options and for the breakdown of novel therapies, as outlined in Table 28.

Table 28: Subsequent treatment proportions for those who receive subsequent treatment

Subsequent treatment option	TRANSFORM Liso-cel	Expert Liso-cel	TRANSFORM SOC	Expert SOC
ASCT	9.38%	1.25%	0.00%	1.25%
Allo-SCT	25.00%	3.75%	3.08%	3.00%
3L+ chemotherapy	100.00%	15.00%	35.38%	11.75%
Other novel therapy	0.00%	81.25%	0.00%	54.75%
3L+ CAR T	0.00%	0.00%	93.85%	66.25%
3L+ radiotherapy	12.50%	0.00%	0.00%	11.75%
Other novel therapy breakdown	PolaBR	Glofitamab	Lon-Tes	Epcoritamab
Company expert estimates – liso-cel (not used by company due to 0% above)	12.3%	40.0%	7.7%	40.0%
NHS England – liso-cel*	0/44 (0%)	35/44 (80%)	2/44 (4%)	7/44 (16%)
Company expert estimates – SOC (not used by company due to 0% above)	16.9%	36.5%	10.0%	36.5%
NHS England – SOC**	0/225 (0%)	157/225 (70%)	33/225 (15%)	35/225 (15%)

* based on data for people receiving treatment after no prior CAR T or 3L CAR T.
** based on data for people receiving treatment after 2L CAR T.

Pola: presumed not used due to earlier line use; Glo range: 07/09/2023 – 17/07/2024 plus 16 prior EAMS patients; Lon range: 17/12/2023 – 17/07/2024; Epco range: 01/02/2024 – 17/07/2024

3.2.8.4 Health state costs and resource use

Health state resource use was applied based on clinical experts consulted by the company. CS Table 63 and 64 details a breakdown of the health state resources and costs applied in the model. The EAG considers the resource use unit costs were appropriately sourced.

3.2.8.5 Adverse event costs and resource use

AE costs were applied separately for each arm based on incidence reported in the TRANSFORM trial.

For liso-cel, AE costs were assumed to be included in the CAR T tariff costs with the exclusion of costs associated with the management of hypogammaglobulinaemia.

For SOC, costs were applied for all Grade ≥ 3 AEs that occurred in >5% of patients.and all grade AESI namely CRS, neurotoxicity and hypogammaglobulinaemia. Costs included in the model for the management of AEs in the SOC arm are outlined in CS Table 65.

Costs associated with neurotoxicity events were granularly applied in the SOC group. A breakdown of the cost associated with the management of neurotoxicity is outlined in CS Table 66, whilst costs associated with managing hypogammaglobulinaemia are in CS Table 67.

The company does not apply AE costs at 2L liso-cel with the assumption that such costs are covered by CAR T tariff. Indeed, as reported in Section 3.2.8.1.1 CAR T tariff include pre-treatment costs, treatment administrative costs and post-infusion costs including AEs occurring 100 days after infusion. In effect, this excludes adverse events occurring beyond this point from being included in the model. However, for SOC CAR T tariffs were applied to patients receiving CAR T at 3L, in addition to the modelling of AE costs that occurred as observed within the trial follow-up. The EAG considers this may be double counting AEs for SOC, whilst underrepresenting them for liso-cel.

Given the implicit assumption that AE costs are not accounted at 3L+, applying the full costs of CAR T with no adjustments for excluding AEs biases the ICER in favour of liso-cel. From the CEM submitted by the company, the £41,010 CAR T tariff applied in the base case includes an estimated AE cost of £10,611. The EAG argues this cost should not be included in the CAR T tariff at 3L+ patients receiving CAR T to align with the company base case assumption of not including AE costs at 3L for liso-cel, and thus excludes this cost in the EAG base case.

3.2.8.6 End of life care costs

Patients who died in the CEM within 5 years are assumed to incur end of life care costs of £10,687 based on PSSRU hospital care estimates (2022). Those who survived beyond 5 years are assumed to incur no costs.

3.3 *Severity modifier*

No severity modifier was applied in the company base case, and the EAG agree with this conclusion.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

Under the company's base case assumptions, liso-cel dominated SOC with a cost reduction of [redacted] and incremental QALY of [redacted]. The company deterministic base case cost-effectiveness results are presented in Table 29.

Table 29: Company base case deterministic results

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NHB at £20,000/ QALY	NHB at £30,000/ QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	[redacted]	-				

4.2 *Company's sensitivity analyses*

The company conducted a series of deterministic sensitivity analyses to explore which parameters were most influential on the ICER. Those most influential were the proportion receiving subsequent treatment in SOC arm, and those receiving subsequent CAR T (see CS Figure 56).

The company also conducted probabilistic sensitivity analyses (PSA) by simultaneously varying different model parameters in a Monte Carlo simulation to explore the impact of parameter uncertainty on their base case. The conclusions of the base case were unchanged. Liso-cel was associated with a cost reduction of [redacted] and incremental QALYs of [redacted] compared to SOC. The company probabilistic base case cost-effectiveness results are presented in Table 30. Visual representation of the PSA can be found in CS Figures 54-55.

Table 30: Probabilistic base-case results

	Total costs	Total QALY	Incremental Costs	Incremental QALYs	ICER	NHB at £20,000/ QALY	NHB at £30,000/ QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]				

The company also undertook a series of scenario analyses, exploring the impact of alternative assumptions and inputs on the cost-effectiveness results. None of the scenarios changed the conclusions of the base case. There is only in one scenario using alternative distributions for subsequent therapies, and alternative OS extrapolations where the incremental costs get relatively close to zero, however liso-cel remains dominant. Detailed results can be found in CS Table 79.

4.2.1 Company PFS2 Implementation

Following the EAG's request to explore using PFS2 in the economic model, the presented a preferred analyses based on this approach to modelling. Resource use was based on EFS curve while health outcomes were based on the PFS-2 curve. The company deterministic and probabilistic base case results from this scenario is presented in Table 31 and Table 32 below.

Table 31: Deterministic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	Dominant	2.65
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.59

Table 32: Probabilistic results (liso-cel PAS price)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	Dominant	2.51
1	Clarification question, B.3: Application of PFS-2 to model QALY benefits	[redacted]	[redacted]	Dominant	2.55

4.3 *Model validation and face validity check*

The EAG conducted validation checks on the model and it appears to reflect the modelling reported in the company submission.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *Exploratory and sensitivity analyses undertaken by the EAG*

5.1.1 Exploratory Analyses

The EAG undertook a series of analyses to explore the impact of their preferred changes to the company base case.

EAG01: Pre-event health state changed from EFS to PFS-2 to better represent the health states of this disease. (Section 3.2.2 and 3.2.6)

EAG02: Weibull distribution used for liso-cel PFS-2 and the loglogistic distribution used for SOC PFS-2 based on reasons outlined in Section 3.2.6.2.

EAG03: Discount applied per weekly cycle for first 5 years of model, rather than annually (Section 3.2.5)

EAG04: Using the log-logistic distribution for liso-cel OS and SOC OS where parameter estimates have come from methods outlined in Section 3.2.6.3.

EAG05: Generalised gamma EFS distribution is assumed for liso-cel TTNT and log-normal distribution is assumed for SOC TTNT where parameters for the chosen distribution is re-estimated following methods outlined in Section 3.2.6.4

EAG06: Bridging therapy changed to better reflect UK practice as detailed in Section 3.2.8.1.2.

EAG07: Adverse events costs removed for 3L CAR T in SOC group for consistency as discussed in Section 3.2.8.5.

EAG08: Subsequent therapy distributions changed to better reflect UK practice as outlined in Section 3.2.8.3

EAG09: Utility values changed from company base case (0.852) to estimates used in NICE TA895 (0.785) as discussed in Section 3.2.7.

EAG10: Starting age of the model changed from [redacted] to 59 to align with the starting age used in NICE TA895 and current data for 2L axi-cel use in CDF.

The individual and cumulative effect of these changes is presented in Table 33.

Table 33: Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Assumption	Reported section	ICER(£/QALY)
Company base case	N/A	-£29,314 (SOC dominated)
EAG01: Use PFS2 for model health state occupation	Section 3.2.2 and Section 3.2.6	-£30,589 (SOC dominated)
EAG02: Use Weibull and log-logistic PFS2 curves for liso-cel and SOC respectively.	Section 3.2.6.2	-£30,961 (SOC dominated)
EAG03: Discount applied per cycle.	Section 3.2.5	-£27,986 (SOC dominated)
EAG04: log-logistic parameters re-estimated and used for liso-cel & SOC OS	Section 3.2.6.3	-£23,149 (SOC dominated)
EAG05: log-normal and generalised gamma parameters re-estimated and used for SOC and liso-cel TTNT respectively	Section 3.2.6.4	-£36,540 (SOC dominated)
EAG06: Bridging therapy changed	Section 3.2.8.1.2	-£27,656 (SOC dominated)
EAG07: AE costs removed for 3L CAR T	Section 3.2.8.5	-£24,130 (SOC dominated)
EAG08: Subsequent therapy changed including proportion in SOC receiving CAR T at 3L	Section 3.2.8.3	£38,126
EAG09: Utility changed for pre-progression state	Section 3.2.7	-£26,078 (SOC dominated)
EAG10: Starting age of model changed	Section 3.2.3	-£31,806 (SOC dominated)
Cumulative		£38,638

5.2 *EAG's preferred assumptions*

The EAG base case deterministic result show an incremental cost [redacted] and QALYs of [redacted]. The ICER for the base case is £38,563. A more detailed summary of the base case is presented in Table 34 below.

Table 34: EAG Deterministic results (liso-cel PAS price)

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NMB at £20,000/QALY
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	£38,638	[redacted]
SoC	[redacted]	[redacted]	-			

The EAG base case assumptions was subject to 500 iterations resulting in an incremental cost of [redacted] and QALYs of [redacted]. The probabilistic sensitivity analyses resulted in an ICER of £41,643.

Table 35 EAG Probabilistic results (liso-cel PAS price)

Treatment	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	NMB at £20,000/QALY WTP threshold
Liso-cel	[redacted]	[redacted]	[redacted]	[redacted]	£41,812	[redacted]
SoC	[redacted]	[redacted]	-			

The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 12 and Figure 13, respectively.

Figure 12: Cost-effectiveness plane (EAG) liso-cel (PAS price) versus SOC

Figure 13: Cost-effectiveness acceptability curve (EAG): liso-cel (PAS price) versus SOC

5.3 *EAG additional analyses*

The EAG conducted a series of analyses building from their base case to explore the impact of the areas of key uncertainty. The following scenarios were explored:

Scenario 1: Vary proportion of patients receiving subsequent CAR T for SOC by 15% (i.e. +/- 15% around preferred clinician estimate of [redacted]%)

Scenario 2: starting age increased to 65 to explore the potential impact of an older liso-cel population.

Scenario 3: Proportion receiving other 3L novel treatment for in the SOC group varied by 15% (i.e. +/- 15% around preferred clinician estimate of [redacted]%)

Scenario 4: Exponential model used for liso-cel OS, as most plausible model fitted to liso-cel trial data.

All EAG base case assumptions were maintained unless affected by scenario explored. The results are shown in Table 36.

Table 36: EAG scenario analyses

Scenario	Δ Cost	Δ QALYs	ICER
EAG Base Case	[redacted]	[redacted]	£38,638
Scenario 1 - Change Subsequent CAR T after 2L SOC	[redacted]	[redacted]	
+15% [redacted]			£24,357
-15% [redacted]			£52,920
Scenario 2 - Model age 65	[redacted]	[redacted]	£46,975
Scenario 3 Chance Subsequent Novel Therapies after 2L SOC	[redacted]	[redacted]	
+15% [redacted]			£34,635
-15% [redacted]			£42,642
Scenario 4 Exponential OS for liso-cel	[redacted]	[redacted]	£27,367

5.4 *Conclusions of the cost effectiveness section*

The company present a model that is consistent in structure with previous appraisals, however can be improved upon through the use of the PFS2 outcome instead of EFS. The company's analysis contains numerous inputs from the TRANSFORM trial which often come from insufficient follow-up and are not representative of UK care, distorting in particular the costs associated with SOC.

The EAG provides an analysis which it considers more reflective of UK practice, however considerable uncertainty remains over the impact on costs and efficacy of second line CAR T or SOC and the subsequent therapies received.

6 References

1. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, *et al.* Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;**26 Suppl 5**:v116-25. http://dx.doi.org/10.1093/annonc/mdv304
2. NHS Digital. *Cancer incidence and mortality*. 2022. URL: https://www.cancerdata.nhs.uk/incidence_and_mortality (Accessed 12 July 2024).
3. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBdO, Berti E, *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* 2022;**36**(7):1720-48. http://dx.doi.org/10.1038/s41375-022-01620-2
4. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;**127**(20):2375-90. http://dx.doi.org/10.1182/blood-2016-01-643569
5. HMRN. *United Kingdom incidence estimates*. York: University of York; 2024. URL: https://hmrn.org/statistics/incidence/uk (Accessed 15th May 2024).
6. CRUK. *Diffuse large B cell lymphoma*. London: Cancer Research UK. URL: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma#:~:text=Each%20year%20about%205%2C000%20people,%25)%20of%20NHL%20in%20adults).
7. HMRN. *Prevalence*. York: University of York; 2024. URL: https://hmrn.org/statistics/prevalence (Accessed 12th May 2024).
8. Deng M, Xu-Monette ZY, Pham LV, Wang X, Tzankov A, Fang X, *et al.* Aggressive B-cell Lymphoma with MYC/TP53 Dual Alterations Displays Distinct Clinicopathobiological Features and Response to Novel Targeted Agents. *Mol Cancer Res* 2021;**19**(2):249-60. http://dx.doi.org/10.1158/1541-7786.Mcr-20-0466
9. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. *Blood Rev* 2017;**31**(2):37-42. http://dx.doi.org/10.1016/j.blre.2016.09.004
10. Li S, Lin P, Medeiros LJ. Advances in pathological understanding of high-grade B cell lymphomas. *Expert Review of Hematology* 2018;**11**(8):637-48. http://dx.doi.org/10.1080/17474086.2018.1494567
11. Kurz KS, Kalmbach S, Ott M, Staiger AM, Ott G, Horn H. Follicular Lymphoma in the 5th Edition of the WHO-Classification of Haematolymphoid Neoplasms-Updated Classification and New Biological Data. *Cancers (Basel)* 2023;**15**(3):785. http://dx.doi.org/10.3390/cancers15030785
12. Hamlin PA, Zelenetz AD, Kewalramani T, Qin J, Satagopan JM, Verbel D, *et al.* Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. *Blood* 2003;**102**(6):1989-96. http://dx.doi.org/10.1182/blood-2002-12-3837
13. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, *et al.* Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010;**28**(27):4184-90. http://dx.doi.org/10.1200/jco.2010.28.1618
14. Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JW, Huijgens PC, *et al.* Health-related quality of life and persistent symptoms in relation

to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry. *Ann Hematol* 2014;**93**(10):1705-15. http://dx.doi.org/10.1007/s00277-014-2099-8
15. Hensel M, Egerer G, Schneeweiss A, Goldschmidt H, Ho AD. Quality of life and rehabilitation in social and professional life after autologous stem cell transplantation. *Ann Oncol* 2002;**13**(2):209-17. http://dx.doi.org/10.1093/annonc/mdf031
16. Myers RM, Hill BT, Shaw BE, Kim S, Millard HR, Battiwalla M*, et al.* Long-term outcomes among 2-year survivors of autologous hematopoietic cell transplantation for Hodgkin and diffuse large b-cell lymphoma. *Cancer* 2018;**124**(4):816-25. http://dx.doi.org/10.1002/cncr.31114
17. Bal S, Costa LJ, Sauter C, Litovich C, Hamadani M. Outcomes of Autologous Hematopoietic Cell Transplantation in Diffuse Large B Cell Lymphoma Refractory to Firstline Chemoimmunotherapy. *Transplant Cell Ther* 2021;**27**(1):55.e1-.e7. http://dx.doi.org/10.1016/j.bbmt.2020.09.004
18. Smeland K, Holte H, Fagerli UM, Bersvendsen H, Hjermstad MJ, Loge JH*, et al.* Total late effect burden in long-term lymphoma survivors after high-dose therapy with autologous stem-cell transplant and its effect on health-related quality of life. *Haematologica* 2022;**107**(11):2698-707. http://dx.doi.org/10.3324/haematol.2021.280413
19. Mendelson E, Nast J, D'Alessio D, Aasaithambi S, Chauhan J, Samavedam S. PCN328 UNDERSTANDING OF PATIENT EXPERIENCE WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) THROUGH SOCIAL MEDIA LISTENING. *Value in Health* 2020;**23**:S82. http://dx.doi.org/10.1016/j.jval.2020.04.1788
20. Lin VW, Oak B, Snider JT, Epstein J. Health-related quality of life (HRQOL) burden in patients with relapsed/refractory diffuse large B-cell lymphoma (RR-DLBCL) and non-Hodgkin's lymphoma (RR-NHL). *Journal of Clinical Oncology* 2020;**38**.
21. National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology (NCCN Guidelines) - B-Cell Lymphomas Version* National Comprehensive Cancer Network; 2023. URL: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf (Accessed 8th February 2024).
22. Sarkozy C, Sehn LH. Management of relapsed/refractory DLBCL. *Best Pract Res Clin Haematol* 2018;**31**(3):209-16. http://dx.doi.org/10.1016/j.beha.2018.07.014
23. BMS. Data on File: TRANSFORM CSR: October 2023 DCO. In; 2023.
24. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N*, et al.* Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. *New England Journal of Medicine* 2022;**386**(7):629-39. https://dx.doi.org/10.1056/NEJMoa2116596
25. Juno Therapeutics aSoC. *Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006)*. 2023. URL: https://classic.clinicaltrials.gov/ct2/show/NCT03483103 (Accessed 9th February 2024).
26. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V*, et al.* Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood* 2023;**141**(14):1675-84. http://dx.doi.org/10.1182/blood.2022018730
27. NICE. *Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]. Final appraisal*

committee papers London: National Institute for Health and Care Excellence 2023. URL: https://www.nice.org.uk/guidance/ta895/documents/committee-papers-2. (Accessed 05 April 2024).
28. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E*, et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;**32**(27):3059-68. http://dx.doi.org/10.1200/jco.2013.54.8800
29. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V*, et al.* Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet* 2022;**399**(10343):2294-308. http://dx.doi.org/10.1016/s0140-6736(22)00662-6
30. FDA. *Lisocabtagene maraleucel (Breyanzi)* Silver Spring (MD): U.S. Food and Drug Administration; 2022. URL: https://www.fda.gov/media/159602/download?attachment).
31. Dahiya S, Spiegel JY, Lee D, Mohammed T, Lutfi F, Goyal A*, et al.* Second-Line Chimeric Antigen Receptor T Cell Therapy (CAR-T) As Standard of Care for Relapsed-Refractory Large B-Cell Lymphoma (LBCL). *Blood* 2023;**142**:4876.
32. Koff JL, Larson MC, Martin P, Cohen JB, Ayyappan SR, Link BK*, et al.* LEO Consortium for Real World Evidence (CReWE): Outcomes after Second-Line Therapy in Large B-Cell Lymphoma By Treatment Era. *Blood* 2023;**142**:307.
33. Yamshon S, Gribbin C, Alhomoud M, Chokr N, Chen Z, Demetres M*, et al.* Safety and Toxicity Profiles of CAR T Cell Therapy in Non-Hodgkin Lymphoma: A Systematic Review and Meta-Analysis. *Clin Lymphoma Myeloma Leuk* 2024;**24**(6):e235-e56.e2. http://dx.doi.org/10.1016/j.clml.2024.02.007
34. CADTH. *CADTH Reimbursement Review Lisocabtagene Maraleucel (Breyanzi)*. Ottawa, ON Canada's Drug Agency 2022. URL: https://canjhealthtechnol.ca/index.php/cjht/article/view/PG0258r/949).
35. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J*, et al.* Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020;**396**(10254):839-52. http://dx.doi.org/10.1016/s0140-6736(20)31366-0
36. Sehgal A, Hoda D, Riedell PA, Ghosh N, Hamadani M, Hildebrandt GC*, et al.* Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol* 2022;**23**(8):1066-77. http://dx.doi.org/10.1016/s1470-2045(22)00339-4
37. Makita S, Yamamoto G, Maruyama D, Asano-Mori Y, Kaji D, Ananthakrishnan R*, et al.* Phase 2 results of lisocabtagene maraleucel in Japanese patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. *Cancer Med* 2022;**11**(24):4889-99. http://dx.doi.org/10.1002/cam4.4820
38. Morschhauser F, Dahiya S, Palomba ML, Martin Garcia-Sancho A, Reguera Ortega JL, Kuruvilla J*, et al.* Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. *Nature Medicine* 2024. http://dx.doi.org/10.1038/s41591-024-02986-9
39. CADTH. *CADTH Search Filters Database*. Ottawa; 2024. URL: https://searchfilters.cadth.ca (Accessed 2024-7-17).

40. CRD. *Search strategies*. York: Centre for Review and Dissemination; 2014. URL: https://www.crd.york.ac.uk/crdweb/searchstrategies.asp (Accessed 17 July 2024).
41. McKinlay RJ, Wilczynski NL, Haynes RB, the Hedges T. Optimal search strategies for detecting cost and economic studies in EMBASE. *BMC Health Services Research* 2006;**6**(1):67. http://dx.doi.org/10.1186/1472-6963-6-67
42. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. PERFORMANCE OF OVID MEDLINE SEARCH FILTERS TO IDENTIFY HEALTH STATE UTILITY STUDIES. *Int J Technol Assess Health Care* 2017;**33**(4):472-80. http://dx.doi.org/10.1017/s0266462317000897
43. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A*, et al.* Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *New England Journal of Medicine* 2023;**389**(2):148-57. https://dx.doi.org/10.1056/NEJMoa2301665
44. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO*, et al.* Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood* 2023;**141**(19):2307-15. http://dx.doi.org/10.1182/blood.2022018893
45. Maurer MJ, Ghesquières H, Jais JP, Witzig TE, Haioun C, Thompson CA*, et al.* Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014;**32**(10):1066-73. http://dx.doi.org/10.1200/jco.2013.51.5866
46. Kearns B, Stevenson MD, Triantafyllopoulos K, Manca A. The Extrapolation Performance of Survival Models for Data With a Cure Fraction: A Simulation Study. *Value in Health* 2021;**24**(11):1634-42. http://dx.doi.org/https://doi.org/10.1016/j.jval.2021.05.009
47. Grant TS, Burns D, Kiff C, Lee D. A Case Study Examining the Usefulness of Cure Modelling for the Prediction of Survival Based on Data Maturity. *PharmacoEconomics* 2020;**38**(4):385-95. http://dx.doi.org/10.1007/s40273-019-00867-5
48. Portuguese AJ, Albittar A, Huang JJ, Liang EC, Wuliji N, Taheri M*, et al.* Real-World Comparison of Lisocabtagene Maraleucel (Liso-Cel) and Axicabtagene Ciloleucel (Axi-Cel): Efficacy & Toxicity. *Transplantation and Cellular Therapy* 2024;**30**(2, Supplement):S192. http://dx.doi.org/https://doi.org/10.1016/j.jtct.2023.12.249
49. Oluwole OO, Chen JMH, Chan K, Patel AR, Jansen JP, Keeping S*, et al.* Matching-adjusted indirect comparison of axi-cel and liso-cel in relapsed or refractory large B-cell lymphoma. *Leukemia & Lymphoma* 2022;**63**(13):3052-62. http://dx.doi.org/10.1080/10428194.2022.2113526
50. Oluwole OO, Neelapu SS, Ray MD, Limbrick-Oldfield EH, Wade SW, Kanters S*, et al.* Network meta-analysis of CAR T-Cell therapy for the treatment of 3L+ R/R LBCL after using published comparative studies. *Expert Review of Anticancer Therapy* 2024;**24**(6):457-65. http://dx.doi.org/10.1080/14737140.2024.2343801
51. Gallacher D. SurvInt: a simple tool to obtain precise parametric survival extrapolations. *BMC Medical Informatics and Decision Making* 2024;**24**(1):76. http://dx.doi.org/10.1186/s12911-024-02475-6
52. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics* 2023;**41**(2):199-207. http://dx.doi.org/10.1007/s40273-022-01218-7

53. National Institute for Health and Care Excellence (NICE). *Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy (TA895). Available at: https://www.nice.org.uk/guidance/ta895. [last accessed 2nd January 2024].*).
54. BMS. TRANSFORM EQ-5D analysis (October 2023 DCO). In.,
55. Boyle S, Roddie C, O'Reilly M, Menne T, Norman J, Gibb A*, et al.* Improved outcomes of large B-cell lymphoma patients treated with CD19 CAR T in the UK over time. *Br J Haematol* 2024;**204**(2):507-13. http://dx.doi.org/10.1111/bjh.19157

7 Appendices

7.1 *Appendix 1: ROBIS assessment of the company SLR*

Table 37: EAG assessment of risk of bias of the CS systematic review of clinical effectiveness

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably no	The EAG are not aware of any pre-published protocol for the company SLR. The SLR was part of a wider review, there were changes made to searches and eligibility criteria at various updates and it is unclear if these were made *a priori* and whether excluded studies were rescreened according to new criteria. An additional set of criteria were used to select only the one relevant trial and this was not explicitly stated *a priori.* Furthermore, the company provided clarification [CQ A5] that studies were also excluded due to reasons not specified in

		the eligibility criteria. For example studies were excluded for 'other' reasons such as having few eligible patients, being protocols with no results, or not being relevant to the topic of the SLR.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The initial set of criteria presented in CS appendix Table 15 are appropriate for the wider review question. The criteria relevant to the decision problem were narrowed down in the CS to only include patients eligible for SCT with relapsed or refractory disease, compared with reinduction therapies R-DHAP, R-ICE and R-GDP. Therefore, this changed the CS inclusion to only one relevant trial from the SLR.
1.3 Were eligibility criteria unambiguous?	Probably yes	The eligibility criteria were generally unambiguous with the exception of the minimum sample size. The company's study design criteria require a minimum sample size by treatment arm (≥25 patients) or per study (≥50 patients). However, there's an inconsistency in how this criterion was applied. For

		example, a single-arm study with ≥26 patients was excluded because it does not meet the ≥50 patients per study criterion, even though it meets the ≥25 patients per treatment arm criterion. This inconsistency has the potential for studies being excluded inappropriately.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	CS appendix Table 15 specifies exclusion of articles published prior to 2003 and conference abstracts prior to 2017 with the rationale provided which appears appropriate. However, the reason for limiting sample size to 50 patients (25 per arm) is not provided, it is unclear whether this is appropriate
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No.	In the search, no language limits are applied. However, during screening only articles in English are included and all other languages excluded. While this may introduce bias of missing out articles in other languages, the restrictions are appropriate for this type of SLR.

Concerns regarding specification of study eligibility criteria	Unclear concern.	Effort has been made to clearly specify the review question and objectives. However, there is lack of clarity in how eligibility criteria were set and adhered to, particularly the EAG could not identify a pre-published protocol, changes to eligibility criteria, inconsistency in applying sample size criteria and potential language restrictions during screening suggest potential risks of bias.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes.	Searched Medline, Embase, Cochrane Central, proceedings of 8 named conferences, 3 trials registries and FDA and EMA websites (CS Appendix D.1.1.2).
2.2 Were methods additional to database searching used to identify relevant reports?	Probably Yes	Additional search methods were used such as grey literature searching and hand searches. Grey literature was sought and reported in Table 12 (CS Appendix D.1.1.2). The search terms are reported but the numbers of results retrieved are not reported in the search strategy, however the numbers reported to have been identified in the PRISMA-Flow diagram

		(CS Appendix D.2 Figure 1) signifies a comprehensive search. Additional searches of Medline, Embase, DARE and the Cochrane DSR were undertaken to identify systematic reviews and these reviews were hand-searched to identify further reports. Page 9 of the CS Appendix states 'Bibliographic handsearching of published SLRs for any further relevant records was also undertaken as part of the SLR'; however, full details of the supplementary searches or reviews, guidelines and grey literature examined are not reported.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No	The update searches (CS Appendix D.1.1.1 Tables 1-8) are sufficiently comprehensive and include terms for the population of interest only. A broad range of free text and database-specific terms were used for R/R/ DLBCL) and concepts related to refractory disease, such as drug resistance, non-response, treatment failure or salvage therapy were also included. Filters for observational and non-

		randomised controlled trials appear to be based on the CADTH search filters. The original search (CS Appendix D 1.1.1 Table 9 and 10) is substantially less sensitive and contains major flaws, for example, the limited selection of free text and thesaurus terms, errors in combining search lines, concepts related to refractory disease not being included and thesaurus (MeSH / Emtree) terms being rarely exploded. The update strategy is only applied to records added to databases since April 2019, therefore potentially relevant results published prior to this date are likely to have been missed.
2.4 Were restrictions based on date, publication format, or language appropriate?	No.	The update (June 2020) searches are restricted to records added to databases from April 2019 onwards. Given that the search strategy has been substantially amended since the earlier searches in 2017 and 2019, the EAG believes that the update search should have been applied for the dates up to 2003 to either replace or supplement

		the original search (CS Appendix D.1.1 Search strategy) to ensure that any potentially eligible studies missed by the original search in April 2019 would not have be picked up by the update search. Conference proceedings were sought from 2016 onwards only. A search of older conference proceedings may have identified further trials that were never published, to counter publication bias. There are no restrictions on publication format or language in the search strategies.
2.5 Were efforts made to minimise errors in selection of studies?	Probably Yes.	Record screening was undertaken by two independent reviewers for both title/abstract screening and full text screening for the wider SLR. However, details for the final step of selecting studies to align with the NICE decision problem are not reported.
Concerns regarding methods used to identify and/or select studies	Unclear concern.	While the search included a comprehensive range of databases and additional methods such as grey literature and hand searches, there were notable concerns in the original search strategy and restrictive

		update searches. The original search was less sensitive, contained errors, and did not fully explore relevant terms, while the update searches only included records from April 2019 onwards, potentially missing earlier studies. Additionally, details of supplementary searches and final selection steps were not fully reported, leading to unclear concerns in those areas.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	Yes.	Standardised form used, extraction by one reviewer and verification by a second reviewer.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes.	Characteristics of one study meeting the decision problem were presented in the main report or Appendix. The other included studies were also tabulated.
3.3 Were all relevant study results collected for use in the synthesis?	No	Only one study was selected after conducting the SLR. The relevance of other studies identified in this review is unclear.
3.4 Was risk of bias (or methodological quality) formally	Probably yes.	The methodological quality of the included non-randomised clinical trials (i.e., single-arm trials and observational studies) was

assessed using appropriate criteria?		assessed using the modified Downs and Black checklist. However, this has not been provided by the company. For randomised controlled trials (RCTs), the NICE recommended questions to assess risk of bias were used.
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably yes.	All quality and risk of bias assessment were validated by a second reviewer and conflicts resolved by a third reviewer.
Concerns regarding methods used to collect data and appraise studies	Unclear concern.	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted in line with the scope. However, the CS did not present all of the studies as some were selected out using another set of criteria.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Yes	The company included all the relevant studies
4.2 Were all predefined analyses followed or departures explained?	No information.	There were no pre-defined analyses specified in the CS.

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Not applicable.	The company had only identified one eligible head-to-head comparison RCT to inform the clinical evidence. Therefore, no indirect treatment comparisons were conducted for this submission.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Not applicable	See above
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable, see 4.3.	Not applicable
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	The review makes no reference to the risk of bias in the trial when discussing the results.
Concerns regarding the synthesis and findings	Some concern	The narrative synthesis did not discuss the ROB in the results.
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	Some concern	The review shows some concerns regarding adherence to predefined objectives and eligibility criteria, ambiguity in eligibility criteria, and unclear

		information regarding predefined analyses. However, efforts were made in data collection, study appraisal, and minimising errors in selection and assessment of studies.

7.2 *Appendix 2: Cochrane RoB 2 assessment by EAG*

Table 38: EAG assessment of risk of bias of TRANSFORM trial

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Permuted-blocks method with a dynamic block size, stratified by response to 1L therapy (refractory versus relapse) and sAAIPI (0–1). Interactive response technology.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN	The CS describes the demographic characteristics as 'reasonably well-balanced', however the EAG notes that the SOC arm had a higher proportion of patients aged under 65 years, with ECOG PS 0 at screening (but not at baseline) and who were men. The implications of this are not clear and the imbalances may be to chance.
	Risk of bias judgement	**Low**	
Bias due to[30] deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PY	The FDA[30] statistical reviewer noted that the EFS endpoint, which included starting a new antineoplastic therapy due to efficacy concerns, could be biased in an open-label trial, as investigators could put more SOC participants into a new

			therapy, either intentionally or unintentionally. However, it was noted that a similar number of participants in each arm met this EFS component. The high proportion of crossover from SOC to liso-cel could suggest investigator bias towards liso-cel. Approaches to censor or not censor people who crossed over can also introduce bias. See section 2.2.8 for further comment on the effects of crossover.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY	Where people who crossed over were censored, the remaining sample was unbalanced. Where censoring did not occur, benefit from crossover was included in the analysis. See section 2.2.8 for further comment.
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N	The protocol did not allow crossover from liso-cel arm to SOC
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data available for the primary and key secondary outcomes. Note that only around half of participants formed the HRQoL set (baseline and at least one post-baseline HRQoL), but this was similar between treatment arms (CSR Table 14.1.2.1). Compliance rates varied across the different measures throughout the study
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Objective measures using defined criteria
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Open-label study, but efficacy assessed by an independent review committee.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Unlikely, objective measures using defined criteria, assessed by an independent review committee.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	The study protocol states that details were described in the statistical analysis plan. This was not initially provided to the EAG but was provided in response to Clarification question A19.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

7.3 *Appendix 3 Additional literature searches undertaken by the EAG*

Run 14th and 17th June 2024

Ovid MEDLINE(R) ALL 1946 to June 14, 2024

1 Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3

(lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA] 36200

2 (Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL] 7781

3 1 or 2 41728

4 Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY] 2683265

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf. 1923

6 (3 and 4) or 5 10021

7 Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-

plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE] 29301

8 Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION] 689511

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf. 59064

10 (1 or 9) and 7 and 8 1355

11 6 or 10 [R/R DLBCL OR TRANSFORMED SUBTYPES] 11104

12 randomized controlled trials as topic/ or clinical trials as topic/ or exp randomized controlled trial/ or clinical trial/ or random allocation/ or double blind method/ or single blind method/ or controlled clinical trial/ or cross-over studies/ or placebos/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kf. [RCTs] 2709114

13 11 and 12 2133

14 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or Non-Randomized Controlled Trials as Topic/ or Controlled Before-After Studies/ or Interrupted Time Series Analysis/ or Historically Controlled Study/ or Control Groups/ or trial.ti. or controlled clinical trial.pt. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT?) or (control$ adj3 ("before and after" or "before after")) or time series or (pre-adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kf. [NON-RANDOMIZED STUDIES] 1655388

15 11 and 14 521

16 Observational study/ or exp Cohort Studies/ or Retrospective Studies/ or Case-Control Studies/ or Cross-Sectional Studies/ or Registries/ or Comparative Study/ or (cohort? or (longitudinal or prospective or retrospective or Cross-Sectional) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison or noncomparative or non-comparative) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or "single arm" or "real world" or registr$).tw,kf. [OBSERVATIONAL] 6289459

17 11 and 16 3591

18 13 or 15 or 17 4839

19 exp Animals/ not (exp Animals/ and Humans/) 5231654

20 18 not 19 4808

21 ((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/) 1500901

22 20 not 21 4776

23 (comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt. 2818454

24 22 not 23 4688

25 2024*.dt,ez,da,ed. 870492

26 24 and 25 219

27 limit 24 to yr="2024 -Current" 213

28 26 or 27 225

29 exp systematic reviews as topic/ or exp meta-analysis as topic/ or exp Technology assessment, biomedical/ or (systematic review or meta analysis).pt. or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence

adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kf. [SRs/NMAs/MAs] 608952

30 11 and 29 207

31 30 not 19 207

32 31 not 21 206

33 32 not 23 204

34 limit 33 to yr="2024 -Current" 19

35 25 and 33 19

36 34 or 35 19

Embase Classic+Embase 1947 to 2024 June 14

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56201

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or

((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14818

3 1 or 2 64865

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3830117

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4772

6 (3 and 4) or 5 24577

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46734

8 cell transformation/ or transform$.tw,kw. 781298

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95519

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26317

12 clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or exp randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or triple blind procedure/ or prospective study/ or "randomized controlled trial (topic)"/ or "clinical trial (topic)"/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kw. 4518024

13 11 and 12 8148

14 exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or time series analysis/ or pretest posttest control group design/ or controlled study/ or control group/ or trial.ti. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT$1) or (control$ adj3 ("before and after" or "before after")) or "time series" or (pre- adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kw. [NON-RANDOMISED RCTs] 11637043

15 11 and 14 10369

16 cohort analysis/ or retrospective study/ or longitudinal study/ or prospective study/ or follow up/ or family study/ or observational study/ or population research/ or exp comparative study/ or exp case control study/ or cross-sectional study/ or register/ or (cohort? or (longitudinal or prospective or retrospective) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or (cross-section$ or crosssection$) or "single arm" or "real world" or registr$).tw,kw. [OBSERVATIONAL] 8686403

17 11 and 16 14183

18 13 or 15 or 17 19057

19 (animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp. 2609963

20 (exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/ 8419450

21 18 not (19 or 20) 18564

22 (exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/)) 3066259

23 21 not 22 18271

24 (editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.)) 3118452

25 23 not 24 17972

26 limit 25 to yr="2024 -Current" 502

27 limit 26 to dc=20240101-20240614 494

28 26 or 27 502

29 systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/ or biomedical technology assessment/ or network meta-analysis/ or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kw. [SRs/NMAs/MAs] 906769

30 11 and 29 667

31 30 not (19 or 20) 662

32 31 not 22 655

33 31 not 24 655

34 limit 33 to yr="2024 -Current" 29

35 limit 32 to dc=20240101-20240617 52

36 34 or 35 52

Cochrane Library

Date Run: 17/06/2024 14:59:06

ID Search Hits

#1 MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] this term only 668

#2 ((large or diffuse*) near/2 (b-cell* or bcell* or "cell b") near/3 (lymphoma* or NHL)):ti,ab,kw 2054

#3 ((diffuse* large or large diffuse*) near/3 (lymphoma* or NHL)) or (histiocytic* near/2 (lymphoma* or NHL)):ti,ab,kw 2492

#4 (("T rex lymphoma" or TINHL or tiNHL) or (T-immunoblastic near/1 NHL) or DLBCL):ti,ab,kw 1365

#5 #1 or #2 or #3 or #4 2561

#6 MeSH descriptor: [Lymphoma, Follicular] this term only 453

#7 (3B or IIIB or three-B or "grade 3"):ti,ab,kw 30825

#8 #6 and #7 70

#9 (second* near/2 (central nervous system or CNS) near/2 (lymphoma* or NHL or involvement or relaps*)):ti,ab,kw 20

#10 (SCNSL or SCNS) or (((follicul* near/2 (lymphoma* or NHL)) or FL) near/2 (3B or IIIB or three-B or "grade 3")):ti,ab,kw 235

#11 (FL3B or 3BFL) or (("high grade" or HG or HGL) near/3 (lymphoma* or NHL)):ti,ab,kw 437

#12 (double hit near/1 (lymphoma* or NHL)) or (MYC near/3 (BCL2 or BCL-2 or BCL6 or BCL-6) near/7 (lymphoma* or NHL)):ti,ab,kw 77

#13 ((primary mediastin* or primary media-stin*) near/4 (lymphoma* or NHL)):ti,ab,kw 1222

#14 ((mediastin* or media-stin* or thymic*) near/2 (b-cell* or bcell* or cell b) near/2 (lymphoma* or NHL)):ti,ab,kw 116

#15 (tFL or "transformed follicular lymphoma" or PMBCL):ti,ab,kw201

#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 2028

#17 #5 or #16 4005

#18 MeSH descriptor: [] explode all trees 0

#19 MeSH descriptor: [] explode all trees 0

#20 MeSH descriptor: [] explode all trees 0

#21 MeSH descriptor: [Recurrence] this term only 16370

#22 MeSH descriptor: [Treatment Failure] explode all trees 4166

#23 MeSH descriptor: [Salvage Therapy] this term only 1006

#24 (recurren* or resistan* or refract* or relaps* or "refractory/relapsed" or recrudescen*):TI,AB,KW 228215

#25 (secondline* or second-line*) or (fail* near/2 (treatment or therap*)) or ((fail* or lack) near/2 respon*) or (nonrespon* or non-respon* or unrespon* or unrespon* or no respon* or (not NEXT respon*)):TI,AB,KW 41109

#26 (reappear* or re-appear* or reoccur* or re-occur*) or (salvage near/2 (therap* or treatment* or regime*)):ti,ab,kw 4242

#27 ((refract* or relaps*) near/3 (b-cell* or bcell* or cell b) near/3 (lymphoma* or NHL)):TI,AB,KW 661

#28 #21 OR #22 OR #23 OR #24 OR #25 OR #26 258324

#29 #17 AND #28 1891

#30 #29 OR #27 2115

#31 MeSH descriptor: [] explode all trees 0

#32 MeSH descriptor: [Leukemia, Hairy Cell] this term only 56

#33 MeSH descriptor: [Waldenstrom Macroglobulinemia] this term only 68

#34 (richter* near/2 (transform* or syndrome*)):TI,AB,KW 129

#35 (("marginal zone" or "mucosa-associated" or MALT) near/3 (lymphoma* or NHL)):ti,ab,kw 440

#36 (maltoma or MZL or (primary cutaneous near/3 (lymphoma* or NHL))):ti,ab,kw 328

#37 (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?):ti,ab,kw 2

#38 Hairy cell* or (leuk?emi* near/2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)):ti,ab,kw 165

#39 (histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) near/2 (lymphoma* or NHL)) or (waldenstrom* near/2 (macroglobulin* or macro-globulin* or macroglobin*)) or ((low-grade or slow* or indolent) near/3 (lymphoma* or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL"):ti,ab,kw 1116

#40 MeSH descriptor: [] explode all trees 0

#41 transform*:ti,ab,kw 12796

#42 (((bcell or b-cell or cell b) near/3 lymphoma*) or ((high grade or aggressive or fast*) near/3 (lymphoma* or NHL)) or ((refract* or relaps*) near/3 lymphoma*)):ti,ab,kw 7998

#43 #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 1783

#44 #5 or #42 8089

#45 #41 and #44 397

#46 #44 and #45 397

Limited to published date studies published in 2024

CENTRAL = 3

ASCO 2024 Conference abstracts

DLBCL 15 results

“Diffuse Large B Cell Lymphoma” 26 results

“Follicular Lymphoma” 20 results

“Primary Mediastinal Large B Cell Lymphoma” 0 results

“High Grade Non-Hodgkin's Lymphoma” 0 results

Embase

"European Society for Medical Oncology".nc. limited to 2023-current 0 results

European Hematology Association – 2024 takes place on 13th16th June 2024

American Society of Hematology conference 2024 takes place December 7-10, 2024

American Association for Cancer Research 2024

“DLBCL”, “Diffuse Large B Cell Lymphoma”, “Follicular Lymphoma”, “Primary Mediastinal Large B Cell Lymphoma”, “High Grade Non-Hodgkin's Lymphoma”, “High-grade B-cell Lymphoma” 26 results

European Organisation for Research and Treatment of Cancer 2024 is held on 10-13th June

International Workshop on non-Hodgkin Lymphoma 2024 is held on 19-24 September 2024

International Conference on Malignant Lymphoma 2024 will be held in July 2024

Clinical.Trials.gov

DLBCL", "Diffuse Large B Cell Lymphoma", "Follicular Lymphoma", "Primary Mediastinal Large B Cell Lymphoma", "High Grade Non-Hodgkin's Lymphoma", "High-grade B-cell Lymphoma" 28 results

World Health Organization Clinical Trials Registry WHO ICTRP

"DLBCL OR Diffuse Large B Cell Lymphoma OR Follicular Lymphoma OR Primary Mediastinal Large B Cell Lymphoma OR High Grade Non-Hodgkin's Lymphoma OR High-grade B-cell Lymphoma"

12 results

Trial RecordsEuropean Union Drug Regulating Authorities Clinical Trials Database

"DLBCL", "Diffuse Large B Cell Lymphoma", "Follicular Lymphoma", "Primary Mediastinal Large B Cell Lymphoma", "High Grade Non-Hodgkin's Lymphoma", "High-grade B-cell Lymphoma" 1 result

Economics and utilities, HRQoL and economic models

Carried out 19th June 2024

Ovid MEDLINE(R) ALL 1946 to June 18, 2024

1 Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf.
36229

2 (Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high

grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. 7787

3 1 or 2 41761

4 Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. 2672314

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf. 1929

6 (3 and 4) or 5 10005

7 Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. 29315

8 Cell Transformation, Neoplastic/ or transform$.tw,kf. 689930

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf. 59115

10 (1 or 9) and 7 and 8 1356

11 6 or 10 11091

12 Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or exp models, economic/ or markov chains/ or monte carlo method/ or exp Decision Theory/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or markov or monte carlo or budget$ or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kf. 773149

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 409886

14 (Economics/ or exp "Costs and Cost Analysis"/ or Economics, Dental/ or exp "Economics, Hospital"/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj1 money) or budget$).ti,ab.) not (((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [MEDLINE - NHS EED Econ filter - tested for performance] 1284782

15 (cost$ or cost benefit analys$ or health care costs).mp. [MEDLINE - Economics - McMaster balanced filter] 941195

16 exp "Costs and Cost Analysis"/ or costs.tw. or cost effective$.tw. [MEDLINE - Costs - McMaster balanced filter] 578986

17 12 or 13 or 14 or 15 or 16 1525262

18 "Cost of Illness"/ or "Length of Stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 267641

19 "Facilities and Services Utilization"/ or Utilization Review/ or Concurrent Review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCE UTILIZATION TERMS] 92682

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - MEDLINE] 1771348

21 11 and 20 265

22 exp Animals/ not (exp Animals/ and Humans/) [ANIMAL STUDIES ONLY - REMOVE - MEDLINE] 5233374

23 (address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE] 2923008

24 21 not (22 or 23) [ANIMAL STUDIES and OPINION PUBLICATIONS - REMOVED - MEDLINE] 263

25 2024*.dt,ez,da,ed. 893960

26 24 and 25 28

27 limit 24 to yr="2024 -Current" 28

28 26 or 27 28

29 Quality-Adjusted Life Years/ 16507

30 (quality adjusted or adjusted life year$).ti,ab,kf. 25685

31 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 15743

32 (illness state? or health state?).ti,ab,kf. 8899

33 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2110

34 (multiattribute$ or multi attribute$).ti,ab,kf. 1468

35 (utility adj3 (score? or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 21646

36 utilities.ti,ab,kf. 10018

37 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,kf. 19101

38 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 6551

39 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 27879

40 (time trade off? or time tradeoff? or tto or timetradeoff?).ti,ab,kf. 2513

41 quality of life/ and ((quality of life or qol) adj (score? or measure?)).ti,ab,kf. 16671

42 quality of life/ and ec.fs. 10964

43 quality of life/ and (health adj3 status).ti,ab,kf. 12479

44 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 7895

45 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change? or impact? or impacted or deteriorat$)).ab. 58562

46 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 5604

47 *quality of life/ and (quality of life or qol).ti. 66288

48 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 45401

49 quality of life/ and health-related quality of life.ti,ab,kf. 48085

50 models,economic/ 11197

51 or/29-50 237888

52 (((vignette? or vignette-based or "vignette based") adj3 (stud$ or descript$)) or ("cross-sectional" adj3 (survey? or questionnaire?))).ti,ab,kf. 87146

53 (AQoL or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or ((15D or 15 Dimension) adj2 utilit$) or ("visual analog scale?" or "visual analogue scale?" or VAS or VAS-pain) or FACIT or FACIT-Fatigue or "FACIT Fatigue" or FACIT-F or "Lee Fatigue" or (LFS adj5 utilit$) or VAS-Fatigue or "Piper Fatigue Scale" or PFS or "Schwartz Cancer Fatigue Scale" or SCFS-6 or FACT or FACT-G or "Functional Assessment of Cancer Therapy" or FACT-Lym or "Functional Assessment of Chronic illness Therapy-Lymphoma" or (FACT-G and (Lymphoma Subscale or LymS)) or "EORTC QLQ-C30" or "EORTC-8D" or "NCCN-FACT FLymSI-18" or AML-QOL or QOL-AML).ti,ab,kf. 433234

54 35 and 53 1825

55 51 or 52 or 54 321425

56 11 and 55 82

57 56 not (22 or 23) 82

58 25 and 57 10

59 limit 57 to yr="2024 -Current" 10

60 58 or 59 10

Embase Classic+Embase <1947 to 2024 June 18>

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex

lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56232

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14822

3 1 or 2 64898

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3831987

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4776

6 (3 and 4) or 5 24588

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2

(macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46749

8 cell transformation/ or transform$.tw,kw. 781772

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95585

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26328

12 economics/ or cost/ or exp health economics/ or budget/ or statistical model/ or probability/ or monte carlo method/ or decision theory/ or decision tree/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or budget$ or markov or monte carlo or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kw. 1956427

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 577665

14 12 or 13 2140495

15 (health economics/ or exp economic evaluation/ or exp health care cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [Embase NHS EED Econ filter - tested for performance] 1932857

16 (cost or costs).tw. 1019661

17 14 or 15 or 16 2773753

18 "cost of illness"/ or "length of stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 465780

19 "facilities and services utilization"/ or health care utilization/ or utilization review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCES UTILIZATION TERMS - Embase] 239647

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - Embase] 3201204

21 11 and 20 1675

22 (exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE] 8257561

23 (editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase] 3513802

24 21 not (22 or 23) 1633

25 limit 24 to yr="2024 -Current" 50

26 limit 24 to dc=20240101-20240619 115

27 25 or 26 115

Embase Classic+Embase <1947 to 2024 June 18>

1 exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex

lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw. 56232

2 (follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw. 14822

3 1 or 2 64898

4 cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw. 3831987

5 ((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw. 4776

6 (3 and 4) or 5 24588

7 marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2

(macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw. 46749

8 cell transformation/ or transform$.tw,kw. 781772

9 (((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw. 95585

10 (1 or 9) and 7 and 8 2928

11 6 or 10 26328

12 economics/ or cost/ or exp health economics/ or budget/ or statistical model/ or probability/ or monte carlo method/ or decision theory/ or decision tree/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or budget$ or markov or monte carlo or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kw. 1956427

13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 577665

14 12 or 13 2140495

15 (health economics/ or exp economic evaluation/ or exp health care cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [Embase NHS EED Econ filter - tested for performance] 1932857

16 (cost or costs).tw. 1019661

17 14 or 15 or 16 2773753

18 "cost of illness"/ or "length of stay"/ or ((cost? adj3 illness$) or ((hospital or length) adj2 stay?)).ti,ab,kw,kf. 465780

19 "facilities and services utilization"/ or health care utilization/ or utilization review/ or (((healthcare or health care) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (health adj3 (resource? or facilit$ or service?) adj3 (utili#ation? or utilise? or utilize? or utili#ing or use$)) or (("continued stay?" or concurrent or utili#ation?) adj3 review?)).ti,ab,kw,kf. [RESOURCES UTILIZATION TERMS - Embase] 239647

20 17 or 18 or 19 [COSTS/ECONOMICS & RESOURCE UTILIZATION TERMS - combined filters - Embase] 3201204

21 11 and 20 1675

22 (exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE] 8257561

23 (editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase] 3513802

24 21 not (22 or 23) 1633

25 limit 24 to yr="2024 -Current" 50

26 limit 24 to dc=20240101-20240619 115

27 25 or 26 115

28 Quality-Adjusted Life Years/ 37761

29 (quality adjusted or adjusted life year$).mp. 51199

30 (qaly$ or qald$ or qale$ or qtime$).mp. 29055

31 (illness state? or health state?).mp. 15675

32 (hui or hui1 or hui2 or hui3).mp. 4446

33 (multiattribute$ or multi attribute$).mp. 1718

34 (utility adj3 (score? or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).mp. 39292

35 utilities.mp. 16254

36 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).mp. 38282

37 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).mp. 10000

38 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).mp. 47771

39 (time trade off? or time tradeoff? or tto or timetradeoff?).mp. 3831

40 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).mp. 35439

41 quality of life/ and ec.fs. 66848

42 quality of life/ and (health adj3 status).mp. 38852

43 (quality of life or qol).mp. and Cost-Benefit Analysis/ 7913

44 ((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change? or impact? or impacted or deteriorat$)).tw. 243581

45 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).mp. 1339

46 *quality of life/ and (quality of life or qol).ti. 117544

47 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).mp. 109504

48 quality of life/ and health-related quality of life.mp. 83772

49 models,economic/ 3639

50 or/28-49 535535

51 (((vignette? or vignette-based or "vignette based") adj3 (stud$ or descript$)) or ("cross-sectional" adj3 (survey? or questionnaire?))).mp. 105062

52 (AQoL or (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6) or ((15D or 15 Dimension) adj2 utilit$) or ("visual analog scale?" or "visual analogue scale?" or VAS or VAS-pain) or FACIT or FACIT-Fatigue or "FACIT Fatigue" or FACIT-F or "Lee Fatigue" or (LFS adj5 utilit$) or VAS-Fatigue or "Piper Fatigue Scale" or PFS or "Schwartz Cancer Fatigue Scale" or SCFS-6 or FACT or FACT-G or "Functional Assessment of Cancer Therapy" or FACT-Lym or "Functional Assessment of Chronic illness Therapy-Lymphoma" or (FACT-G and (Lymphoma Subscale or LymS)) or "EORTC QLQ-C30" or "EORTC-8D" or "NCCN-FACT FLymSI-18" or AML-QOL or QOL-AML).mp. 744667

53 50 or 51 or (52 and 34) 634468

54 11 and 53 431

55 limit 54 to dc=20240101-20240619 49

56 limit 54 to yr="2024 -Current" 22

57 55 or 56 49

International HTA database INAHTA

Lisocabtagene maraleucel 0 results

“DLBCL”, “Diffuse Large B Cell Lymphoma”, “Follicular Lymphoma”, “Primary Mediastinal Large B Cell Lymphoma”, “High Grade Non-Hodgkin's Lymphoma”, “High-grade B-cell Lymphoma”

5 results

Total results pre-duplication: 952

Results post duplication: 757

7.4 *Appendix 4 Sources of prices used in EAG confidential appendix (provided separately)*

Name	Form	Dose per unit	Pack size	Price used in this version of appendix
Liso-cel	N/A	N/A	N/A	PAS discount
Axi-cel	N/A	N/A	N/A	PAS discount
Cyclophosphamide	IV	500.0 mg	1 vial	eMIT (updated 5 April 2024)
Dexamethasone (Oral)	Oral	4.0 mg	50 tablets	eMIT (updated 5 April 2024)
Dexamethasone (IV)	IV	3.3 mg	10 ml	eMIT (updated 5 April 2024)
Cytarabine	IV	100.0 mg/ml	5 ml	eMIT (updated 5 April 2024)
Cisplatin	IV	1.0 mg/ml	100 ml	eMIT (updated 5 April 2024)
Fludarabine	IV	50.0 mg	1 vial	eMIT (updated 5 April 2024)
Rituximab	IV	10.0 mg/ml	20 ml	Midpoint MPSC
Gemcitabine	IV	100.0 mg/ml	10 ml	eMIT (updated 5 April 2024)
Carmustine	IV	100.0 mg	1 vial	eMIT (updated 5 April 2024)
Carboplatin	IV	10.0 mg/ml	45 ml	eMIT (updated 5 April 2024)
Etoposide	IV	20.0 mg/ml	5 ml	eMIT (updated 5 April 2024)
Ifosfamide	IV	2000.0 mg	1 vial	MPSC (nationwide price)
Melphalan	IV	50.0 mg	1 vial	eMIT (updated 5 April 2024)
Bendamustine	IV	100.0 mg	1 vial	eMIT (updated 5 April 2024)
Oxaliplatin	IV	5.0 mg	10 ml	eMIT (updated 5 April 2024)
Methylprednisolone	IV	500.0 mg	1	eMIT (updated 5 April 2024)
Chlorambucil	PO	2.0 mg	25	MPSC (nationwide price)
Lomustine	PO	40.0 mg	20	MPSC (nationwide price)

Epirubicin	IV	2.0 mg	5 ml	eMIT (updated 5 April 2024)
Polatuzumab vedotin	IV	30.0 mg	1 vial	PAS discount
Glofitamab	IV	1.0 mg/ml	2.5 ml	PAS discount
Obinutuzumab	IV	25.0 mg/ml	40.0 ml	PAS discount
Loncastuximab Tesirine	IV	10.0 mg	1 vial	PAS discount
Epcoritamab	IV	4.0 mg	1 vial	PAS discount
Tocilizumab	IV	200 mg	1 vial	Midpoint MPSC
Cuvitru	IV	10g/50ml	1 vial	MPSC (nationwide price)