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

Confidential information redacted

Technology appraisal committee C [14 January 2025]

Chair: Richard Nicholas

External assessment group: Warwick Evidence

Technical team: Kirsty Pitt, Mary Hughes, Ross Dent

Company: Bristol-Myers Squibb

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

- ✓ **Recap**
- ❑ Response to consultation
- ❑ Other considerations

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RECAP

Recap – Committee's key conclusions from ACM1

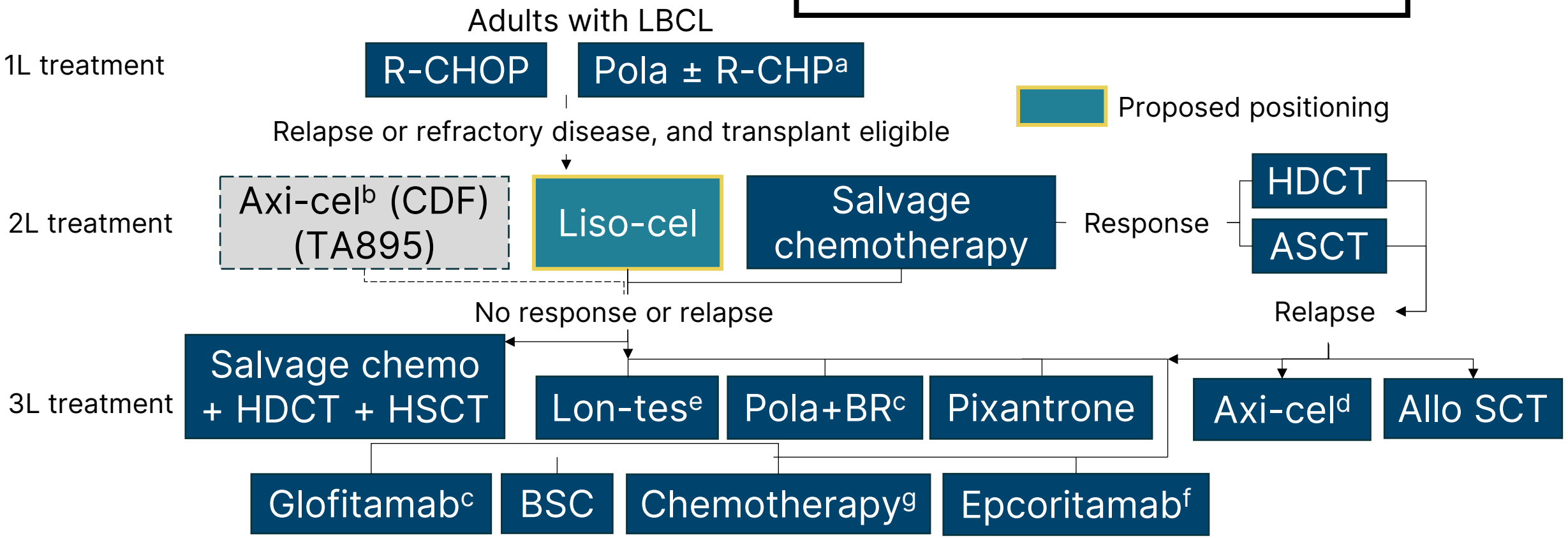
Liso-cel is not recommended

Issue	Committee's preferred assumption (*assumptions with notable uncertainty)
Comparator	Because axi-cel is only available in the CDF in second line, standard care is the relevant comparator
Model structure	Company's model with health states based on event free survival is appropriate
Overall survival*	Company's mixture cure models for liso-cel and standard care
Time to next treatment	Company's extrapolations from TRANSFORM
Model starting age	Company's. Mean age from TRANSFORM
Discounting	EAG's. Per cycle discounting
Utility values*	Company's. Estimated from TRANSFORM, but uncertainty because of low completion rate
Bridging therapy*	Company's. Use TRANSFORM to align costs and benefits, but generalisability concerns
Subsequent treatment*	Clinical experts: up to 80% in both arms have subsequent treatment if disease relapses Company's: distribution of treatments as in TRANSFORM, but generalisability concerns
AE costs at third line	EAG's CAR T tariff cost should be adjusted to remove these→ no AE costs for any 3rd line treatment
CAR T tariff	NHSE: Updated CAR T tariff cost of £58,964 should be used in the model
Acceptable ICER	Around the middle of the normal range (£20,000 to £30,000 per QALY)

Abbreviations: ACM, appraisal committee meeting; CDF, Cancer Drugs Fund; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; AE, adverse event; CAR T, chimeric antigen receptor T cell

Treatment pathway

Clinical expert: Treatment decision would be whether to use axi-cel or liso-cel at 2L



[a] only in people with DLBCL (TA874); [b] only in people with DLBCL (TA895); [c] only in people with DLBCL (TA927 and TA649); [d] only in people with DLBCL or PMBCL (TA872); [e] only in people with DLBCL or HGBCL who have received polatuzumab and are ineligible for treatment with CAR-T (NICE TA947); [f] only in people with DLBCL (TA954); [g]assumed to be 100% R-bendamustine in company's model

Abbreviations: 1L, first line; 2L, second line; 3L, third line; allo SCT, allogeneic stem cell transplant; ASCT, autologous stem cell therapy; axi-cel, axicabtagene ciloleucel; B, bendamustine; BSC, best supportive care; C, cyclophosphamide; CDF, Cancer Drugs Fund; diffuse large B-Cell lymphoma; H, doxorubicin; HDCT, high-dose chemotherapy; HSCT, hematopoietic stem cell transplantation; LBCL: large B-cell lymphoma; liso-cell, lisocabtagene maraleucel; lon-tes, loncastuximab tesirine; O, vincristine; PMBCL, primary mediastinal B-cell lymphoma; pola, polatuzumab vedotin; R, rituximab; P, prednisolone

Lisocabtagene maraleucel (Breyanzi, BMS)

Marketing authorisation	MHRA approved marketing authorisation extension for liso-cel in the indication: 'for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy'
Mechanism of action	Autologous anti-CD19 CAR-T therapy
Administration	• Single dose IV infusion • Must be administered in a qualified treatment centre
Price	• The list price of one dose of liso-cel is £297,000 • A confidential patient access scheme is applicable

Population in appraisal is narrower: adults with early relapsed/primary refractory DLBCL, HGBCL, PMBCL or FL3B **who are eligible for SCT**

Abbreviations: DLBCL; diffuse large B-cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IV, intravenous; liso-cel, lisocabtagene maraleucel; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplantation; CAR T, chimeric antigen receptor T cell

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Summary of consultation responses

Responses received from company, experts, patient organisations and web comments

Consultation responses received from

- Company (see following slides)
- Clinical expert
- Blood Cancer UK
- Lymphoma Action
- Web comments
    - Gilead
    - Clinical expert

Summary of consultation comments from stakeholders [1]
Not including company's comments

Impact of condition on patients

- Significant effect on mental and physical health and quality of life on patients and their loved ones
- Psychological burden and mental strain from fear of relapse and not having suitable treatment available
- Unmet need in second line

NHS CAR-T tariff

Gilead comments:

- Concern that updated cost of CAR T tariff has been agreed without external consultation with relevant stakeholders, and no breakdown of actual costs provided
- May be expected that the costs of delivering CAR T treatment would decrease over time with scale and experience

Web comments from clinician:

- Use of liso-cel will enable quite significant cost savings compared with axi-cel around inpatient stay and ITU use

Current clinical practice

- Dropout rate with second line CAR T is much lower in practice than seen in third line – currently around 9%
- Design of TRANSFORM favours standard care arm with early apheresis and crossover
- Availability of pola R-CHP in first line is likely to mean less requirement for liso-cel in second line
- Draft guidance states that "a third of patients would have palliative treatment in third line" – now would be much lower due to availability of third line bispecifics which can be delivered to much older and less fit patients

Abbreviations: CAR T, chimeric antigen receptor T cell; pola R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone; ITU, intensive therapy unit

Summary of consultation comments from stakeholders [2]
Not including company's comments

Benefits of liso-cel

- Reduced side effects compared with current treatment – currently side effects such as fatigue, sickness, diarrhoea and recurrent infections impact a person's ability to work or carry out normal activities of daily living. Reduced side effects also reduces pressures on hospital capacity.
- Innovative option with curative potential
- One-time treatment early in the pathway avoids numerous cycles of intensive chemotherapy and offers more patients the opportunity of a cure
- Can be given in outpatient setting – would have a huge impact on current capacity in the NHS, release capacity for other cancer surgeries, reduce disruption and travel time for patients, allows patients to be at home longer with loved ones

Comparator

- Comparator of high dose chemotherapy and stem cell transplant is much more toxic and not as effective as liso-cel. Patients are in hospital for 1 month and yet is ineffective in 90% of patients.
- Comparator in practice is axi-cel (CDF) – comparing with salvage chemotherapy, high-dose chemotherapy and a stem cell transplant (now not commonly used) has prevented the committee from realising some of the additional uncaptured benefits of liso-cel
- Axi-cel is an inpatient treatment and people are usually in hospital 10-14 days. 20% of patients require ITU after this which could be for 2 weeks
    - In TRANSFORM, 4% of recipients admitted to ICU compared to 25% in axi-cel's ZUMA-7 trial

Abbreviations: CDF, Cancer Drugs Fund; ICU, intensive care unit; ITU, intensive therapy unit

Overview of company's response

Company's model includes most of committee's preferred assumptions from ACM1

Conclusions in the draft guidance

- Company includes all committee's preferred assumptions in updated base case
  - Except change to 3L AE costs – see below

Additional changes in company's updated base case

- Incorporate costs associated with ICU (NHSE confirmed not included in CAR T or HSCT tariffs)
- Instead of removing 3rd line AE costs from the CAR T tariff, include AE costs for all other 3rd line treatments
- Updated costs for managing 2nd line AE costs in standard care arm
- Increased PAS discount

Company's further scenario analyses

- Company contends that using same tariff for 2nd line liso-cel and 3rd line axi-cel does not capture liso-cel benefits
- Therefore, provides scenario analyses that adjust the CAR T tariff to account for
  - Improved safety profile with liso-cel
  - Outpatient delivery of liso-cel

Abbreviations: ACM1, first appraisal committee meeting; 3L, third line; AE, adverse events; ICU, intensive care unit; NHSE, NHS England; CAR T, chimeric antigen receptor T cell; HSCT, haematopoietic stem cell transplant; PAS, patient access scheme

Key issues

Issue	Slides	ICER impact
Should ICU costs associated with all second-line and third-line treatments be included in the model? If so, should the proportions of people requiring ICU stay after CAR T be taken from real world evidence or trials?	12-13	Small
Should third-line adverse event costs be included by using the full CAR T tariff cost and adding in costs for all other non-CAR T treatments?	14	Small
Should the CAR T tariff be adjusted to take into account lower costs with liso-cel for: • Adverse event management • Outpatient delivery?	15	Large

Abbreviations: ICU, intensive care unit; CAR T, chimeric antigen receptor (CAR) T cell; ICER, incremental cost-effectiveness ratio

Key issues: ICU costs [1]

Small ICER impact

Background

- Not included in original company base case as assumed to be included in NHS CAR T and HSCT tariffs
- After ACM1, NHS England confirmed these are not included

Company

- Revised base case includes ICU costs associated with all 2L and 3L treatments
- Management of grade ≥3 CAR T specific AEs (ICANS) requires ICU admission – expected to be lower with liso-cel than axi-cel
- Revised base case includes ICU costs but not the impact on HRQoL or NHS capacity
- Length of stay was assumed to be equal for axi-cel and liso-cel at 7.5 days, based on clinical opinion in TA872 (axi-cel)
- Model inputs for proportions requiring ICU based on French real-world evidence study – 380 patients having second line axi-cel or liso-cel in hospitals in France (majority axi-cel) (company's unpublished study)

Proportion of patients requiring ICU stay (company base case)

Input	Value	Source
2L treatments		
Liso-cel 2L	[redacted]	French RWE (n=[redacted])
SOC 2L	[redacted]	TRANSFORM
3L treatments		
Axi-cel	[redacted]	French RWE (2L) (n=[redacted])
AutoSCT	[redacted]	TRANSFORM
AlloSCT	[redacted]	Taheri et al. (2019, pts with haematological malignancy) reported ICU rates for allogenic SCT were 2.75x higher than autologous SCT
Radiotherapy	0%	Assumption
Chemo	2.75%	Clinical expert

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Abbreviations: ACM, appraisal committee meeting; ICANS, immune effector cell-associated neurotoxicity syndrome; CAR-T, chimeric antigen receptor (CAR) T cell; RWE, real world evidence; ICU, intensive care unit; (H)SCT, (haematopoietic) stem cell transplant; HRQoL, health-related quality of life; AE, adverse event; TA, technology appraisal; 2L, second line; 3L, third line

Key issues: ICU costs [2]*

Small ICER impact

EAG comments

- EAG agrees including ICU costs is appropriate
- Questions use of RWE study when data from published trials are available (TRANSFORM/ZUMA-7)
  - RWE study sponsored by company, and unpublished
  - Small number of people had liso-cel
- Estimates for % people needing ICU stay with axi-cel in the study are from 2L population but applied in model at 3L (despite RWE being available for 3L population)
- Unclear why majority of the population in the study had axi-cel. Suggests it could be historical data, in which case axi-cel outcomes may have improved with experience more recently.
- Unclear whether the figure from TRANSFORM used for 2L ICU admissions in SC arm includes ICU admissions related to subsequent therapies
  - ➢ EAG prefers to use figure from TRANSFORM for liso-cel as well ([redacted]), in line with approach for SC
  - ➢ EAG would have preferred to use figure for 3L CAR T from TRANSFORM but this was not presented
- Content with assumption of equivalent duration of ICU stay with CAR T, but may be conservative because clinical experts state toxicities with axi-cel may be more difficult to treat

- Should ICU costs associated with all 2L and 3L treatments be included in the model?
- If so, should the proportions requiring ICU stay after CAR T be taken from real world evidence or trials?

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Abbreviations: ICU, intensive care unit; SC standard care; RWE, real world evidence; 2L, second line; 3L, third line; CAR T, chimeric antigen receptor T cell

*see link to trial data

Key issues: Third line adverse event costs

Small ICER impact

Background

- In original base case, the CAR T cell tariff cost was applied to people having subsequent CAR T therapy in the standard-care arm – this includes costs associated with adverse events. For other subsequent therapies, no costs associated with adverse events were included in either treatment arm
- EAG preferred to exclude costs associated with adverse events (estimated by the company as £10,611) from the CAR T cell tariff cost when used for subsequent CAR T therapy (i.e. no subsequent treatment adverse event costs included) - Committee accepted EAG approach in draft guidance

Company

- Considers it more appropriate to use the full CAR T tariff cost but also include adverse event costs for all other non-CAR T third line therapies – costs assumed to be same as for SC in second line (£7,310)

EAG comments

- Costs with alloSCT likely to be much higher than others
- Proportion having alloSCT much higher in liso-cel arm
- Company could have used treatment-specific estimates from TRANSFORM
- EAG takes same approach as company in base case

Subsequent treatment	Liso-cel	SC
Proportion of patients who receive a subsequent treatment	[redacted]	[redacted]
ASCT	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]
3L+ chemotherapy	[redacted]	[redacted]
3L+ radiotherapy	[redacted]	[redacted]
3L+ CAR T	[redacted]	[redacted]

Should third line adverse event costs be included by using the full CAR T tariff cost and adding in costs for all other non-CAR T treatments?

Abbreviations: ICANS, immune effector cell-associated neurotoxicity syndrome; SC, standard care; CAR T, chimeric antigen receptor (CAR) T cell; SCT, stem cell transplant; allo, allogeneic; ASCT, autologous SCT; 3L, third line

Large ICER impact

Key issues: Uncaptured benefits related to use of CAR T tariff

Company

- CAR T tariff currently predominantly reflects the costs associated with axi-cel 3L
- Could be revised downwards in future, when the more favourable safety profile of liso-cel has been observed in clinical practice
- Use of the CAR T tariff (of £58,964) means additional benefits associated with liso-cel cannot be captured in the revised base case - company has provided **scenario analyses** that adjust the CAR T tariff:

1 To reflect liso-cel safety profile
- Based on incidence rates of AEs reported in TRANSFORM and ZUMA-1
- Lower calculated total costs for AE management per patient with liso-cel [redacted] than axi-cel (£20,483)

2 To reflect outpatient delivery of liso-cel
- Company experts' feedback stated would expect to deliver liso-cel in the outpatient setting for 50 - 80% of patients
- Of those, some do have some inpatient monitoring but [redacted] modelled never to have inpatient monitoring

- Further uncaptured benefits unable to be quantified:

Outpatient delivery of liso-cel
Reduced ICU admissions

→

Improved QoL for patients and caregivers
Relieves pressure on NHS bed capacity

EAG note that company's points relate to a comparison of liso-cel and axi-cel at 2L, although the scenario analyses use liso-cel at 2L and axi-cel at 3L. EAG present some further scenarios exploring potential benefit.

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Does a single tariff for CAR-T result in uncaptured benefits for liso-cel?
Are these scenarios appropriate for capturing any uncaptured benefits of liso-cel?

Abbreviations: ICU, intensive care unit; QoL, quality of life; CAR T, chimeric antigen receptor T cell; 2L, second line; 3L, third line; AE, adverse event

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
2L adverse event management costs	Includes updated costs since ACM1 – for standard care arm, increases costs from [redacted] (see back up slide)	Original costs [redacted]
ICU costs	Include from French RWE study (liso-cel and axi-cel)	Include from TRANSFORM for liso-cel
3L adverse event costs	Use the full CAR T tariff cost and include adverse event costs for all other non-CAR T third line therapies	Same as company base case
Company implements all of committee's preferred assumptions from 1st meeting. EAG maintains its preference for:		
Proportion of people having bridging therapy		From Boyle et al. (UK-specific) rather than based on TRANSFORM
Model starting age		NHSE data on people having 2L axi-cel in CDF, rather than mean age in TRANSFORM
Distribution of subsequent therapies		Based on expert opinion rather than TRANSFORM

Abbreviations: ACM, appraisal committee meeting; 2L, second line; 3L, third line; RWE, real world evidence; ICU, intensive care unit; NHSE, NHS England; CDF, Cancer Drugs Fund; CAR T, chimeric antigen receptor T cell

Cost-effectiveness results

All cost-effectiveness estimates are reported in Part 2 slides because they include confidential discounts

Cost-effectiveness results to be presented include:

Scenarios

- Committee's preferred assumptions from ACM1
- Updated company base case
  - Company scenarios amending CAR T tariff to model suggested uncaptured benefits of liso-cel vs. axi-cel
- EAG base case
  - Further EAG scenario analyses

Analyses

- Deterministic
- Probabilistic (base cases)

MPSC prices

- Midpoint MPSC prices for rituximab and tocilizumab

	ICER (£/QALY) versus SC
Company base case	>£30,000
EAG base case	>£30,000
Company scenarios reduce base case ICER	<£30,000 if reduce AE costs in tariff for liso-cel

Note: company concluded that liso-cel is **not eligible** for a severity modifier when compared to standard care, and the EAG agreed

Abbreviations: ICER, incremental cost effectiveness ratio; MPSC, Medicines Procurement and Supply Chain; QALY, quality adjusted life year; SC, standard care; ACM, appraisal committee meeting; CAR T, chimeric antigen receptor T cell; AE, adverse event

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Equality considerations

No further equality considerations raised at consultation

Equality considerations in the draft guidance:

1. Clinicians consider a person's fitness when deciding whether more intensive cancer treatments are suitable for them. A person's age may be used as a proxy for levels of fitness. Age is a protected characteristic under the Equality Act 2010.
2. Stakeholders also commented that there is a geographic inequality because CAR T-cell therapy is only provided at designated centres.

→ The committee noted these concerns but concluded that its recommendation for liso-cel would not adversely affect people protected by the equality legislation.

Abbreviations: CAR T, chimeric antigen receptor T cell

Managed access: committee concluded not appropriate

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company

- Submission is based on the final data cut-off from TRANSFORM and no further data are expected to become available in this patient population to inform decision making

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Back up slides

Key issues: ICU costs – proportions of patients

Small ICER impact

Comparison of proportion of patients requiring ICU admission in French RWE and TRANSFORM/ZUMA-7 trials

	Axi-cel: Proportion requiring ICU admission	Liso-cel: Proportion requiring ICU admission
French RWE Study	[redacted]	[redacted]
Trial (ZUMA-7/TRANSFORM)	25.0%	[redacted]

Abbreviations: ICU, intensive care unit; RWE, real world evidence

Link back to Key issues: ICU costs [2]

Additional company changes to the model

Small ICER impact

Changes to costs of management of adverse events in the standard care arm→ increases total AE management cost in standard care arm (<£2000 change)

Company

Second-line adverse event management costs - sources

- Source of these costs for standard care arm has been updated since submission e.g. neutropenia costs were previously based on NHS reference costs for 'agranulocytosis', now based on 'other haematological or splenic disorder'
- Increases costs from [redacted]

Rehab after ICU-related neurotoxicity

- Added - costed at £710.68 per day (NHS reference costs) for 14 days (expert opinion)
- Applied for all grade ≥3 cases of neurotoxicity
- Increases AE management cost for standard care arm to [redacted]

Ward management costs

- Added for grade 1 and 2 neurotoxicity and CRS
- Increases AE management cost for standard care arm to [redacted]

Adverse event	Old cost (NHS ref costs)	New cost (alternate NHS ref costs)
Neutropenia Prolonged cytopenia	£2,336 £2,708	£1,773
Anaemia	£1,603	£2,801
Febrile Neutropenia	£2,336	£5,622

EAG comments

- Prefers to use original management costs [redacted] because no issue was raised with them previously and there is little justification given for change

Should the original or updated costs be used for managing adverse events in SC arm?

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; ICU, intensive care unit; SC, standard care

Link back to Summary of company and EAG base case