# Single Technology Appraisal

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

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

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

**Contents:**

The following documents are made available to stakeholders:



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

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

**Consultation on the draft guidance document – deadline for comments: 5pm on Thursday 5 December 2024. Please submit via NICE Docs.**

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br><br>• has all of the relevant evidence been taken into account?<br><br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br><br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br><br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br><br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced. |
| **Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):** | **Bristol Myers Squibb** |
| **Disclosure**<br><br>**Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]**<br><br>**Please state:** | **N/A** |

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| • **the name of the company**<br>• **the amount**<br>• **the purpose of funding including whether it related to a product mentioned in the stakeholder list**<br>• **whether it is ongoing or has ceased.** | |
| **Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | **N/A** |
| **Name of commentator person completing form:** | [redacted]<br>[redacted]<br>Bristol Myers Squibb |

| Comment number | Comments<br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| **Executive Summary** | BMS would like to thank NICE for the opportunity to respond to the draft guidance for lisocabtagene maraleucel (liso-cel) for treating large B-cell lymphomas (LBCL) who are refractory to, or have relapsed within 12 months after, first-line chemotherapy when a stem cell transplant is suitable [ID3887]. BMS is extremely disappointed that liso-cel has been issued a negative draft recommendation in this indication and feel strongly that key factors have not been formally captured or considered by the Committee within the appraisal to date, as detailed within this response.<br><br>In this appraisal, BMS is unable to directly compare liso-cel with the most clinically appropriate comparator, axicabtagene ciloleucel (axi-cel), which represents the current standard of care in UK clinical practice in the second-line (2L) LBCL setting. However, as per NICE processes, it is not considered a relevant comparator because it is currently reimbursed via the Cancer Drugs Fund (CDF). As such, this appraisal compares liso-cel with re-induction immunochemotherapy and subsequent high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT), which no longer represent the standard of care (SOC) since the availability of axi-cel via the CDF. This comparison, therefore, fails to capture the highly relevant benefits that are offered by liso-cel over axi-cel in the 2L setting that will not only benefit patients, but could lead to considerable cost-savings for the NHS.<br><br>BMS does not challenge the NICE processes and accepts that axi-cel cannot be a formal comparator in this appraisal in the 2L setting. However, given axi-cel is available via |

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| | routine commissioning at 3L, BMS has revised their base case to capture, where possible, the benefits of liso-cel over axi-cel 3L where it is used in the comparator arm as a subsequent treatment.<br><br>**The key benefit of liso-cel over axi-cel is its more favourable safety profile.**<br><br>Some of these downstream benefits can be formally captured in the economic analysis and are detailed in the revised base case section. However, other benefits cannot, and these are detailed below:<br><br>• A reduction in the costs associated with the management of adverse events (AEs) which cannot be explicitly captured in the economic analysis due to the use of the NHS CAR T tariff (**Issue 3a**).<br><br>• A reduction in the proportion of patients requiring intensive care unit (ICU) admission, typically due to cytokine release syndrome (CRS) and neurological toxicity, would alleviate the substantial costs and healthcare burden associated with such admissions. As ICU costs are not considered in the CAR T tariff, part of this benefit has been directly captured in the revised base case (see **Issue 1**). However, the model is unable to explicitly capture the improvement in health-related quality of life (HRQoL) as a result of the reduced ICU admissions. Additionally, the reduction in ICU admissions would significantly free up valuable ICU bed capacity, allowing for better resource allocation and potentially improving outcomes for other critically ill patients (**Issue 3c**)<br><br>• The potential for liso-cel to be administered and monitored within the outpatient (ambulatory) setting is significant, which CAR T Clinical Experts, interviewed to support this response, are estimating would apply to 50–80% of liso-cel patients[1], Although this benefit cannot be explicitly captured within the economic analysis due to the use of the NHS CAR T tariff, it would provide a substantial cost saving for the NHS and improve HRQoL for patients. Moreover, it would release valuable bed capacity, enhancing overall healthcare efficiency. Outpatient administration and monitoring is not considered suitable with axi-cel owing to its toxicity profile (**Issue 3b**)<br><br>The above benefits are strongly supported by recent feedback from interviews held by BMS with nine CAR T Clinical Experts (referred to as 'Experts feedback') from across England who are experienced in the delivery of CAR T therapies in this indication.[1] The Experts feedback was unanimous in emphasising the magnitude of clinical benefit and cost savings of liso-cel over axi-cel, which are not able to be fully captured within the revised base case and essential for formal consideration by the Committee. A summary report of the Clinical Expert Interviews is presented in **Appendix 1**.<br><br>**Revised base case**<br><br>BMS accept the following Committee-preferred assumptions from ACM1 and have |

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incorporated these into their revised base case:

- Setting the proportion of patients who have subsequent therapy after a *time-to-next-treatment* event to be equal for liso-cel and SOC, assuming a value of 80% as per the Clinical Experts' view in the ACM
    - BMS also validated this assumption during the Clinical Expert Interviews (see **Appendix 1**).
- The CAR T tariff cost has been updated to be £58,964.

In addition, BMS has made the following updates within their revised base case, based on new information from NHS England and the Clinical Expert Interviews:

- **Incorporation of the costs associated with ICU admission** for all 2L and 3L treatments, following confirmation from NHS England that ICU costs are not included within the CAR T or HSCT tariffs (see **Issue 1**)
- **Incorporation of the costs associated with AEs for all 3L treatments,** to ensure that all relevant differences in costs between the two model arms are captured. AE costs for 3L axi-cel are retained via the CAR T tariff and AE costs associated with other 3L therapies have now been incorporated (see **Issue 2)**
- **Incorporation of a revised PAS price for liso-cel** of [redacted]. All other treatments are modelled at list price.

Results of the revised base case are shown below in Table 1.

**Table 1: Revised base case results**

| Treatment | Total costs | Total QALYs | Incr. Costs | Incr. QALYs | ICER | NHB at £20,000/ QALY WTP threshold | NHB at £30,000/ QALY WTP threshold |
|---|---|---|---|---|---|---|---|
| Liso-cel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SOC | [redacted] | [redacted] | | | | | |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

**Summary**

The revised base case underlines the potential for liso-cel to be a cost-effective use of NHS resources. Importantly, this revised base case is unable to capture a number of key benefits associated with liso-cel, primarily as a result of the more favourable safety profile of liso-cel compared with axi-cel and the use of the NHS CAR T tariff. These include: the reduced costs associated with the management of AEs; the impact of reduced ICU admissions on patient's HRQoL and capacity release; and the increased potential for the outpatient delivery of liso-cel in clinical practice. The exclusion of 2L axi-cel as a

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| | comparator within the appraisal further exacerbates this issue, since many of the comparative benefits of liso-cel versus axi-cel can only be partially and indirectly captured, by comparing liso-cel versus 3L axi-cel when used as a subsequent treatment. BMS urges the Committee to consider these uncaptured benefits within their decision making. |
| **Issue 1: Inclusion of ICU costs** | **ICU costs were omitted from the original base case and should be captured in the revised base case of liso-cel**<br><br>In the original base case, the costs associated with ICU resource use (referred to as 'ICU costs') were assumed to be included in the NHS CAR T and HSCT tariffs (used for SOC). However, after the ACM, NHS England confirmed that ICU costs are *not* included in these tariffs. Therefore, the revised base case now includes the ICU costs associated with all 2L and 3L treatments.<br><br>As the management of Grade ≥3 CAR T specific AEs (namely immune effector cell-associated neurotoxicity syndrome or ICANS) would require ICU admission, the lower rates of Grade ≥3 CAR T specific AEs associated with liso-cel compared to axi-cel 3L would translate to reduced ICU admissions. A stay in ICU has a critical impact on both patients and caregivers and it also leads to substantial costs so any reduction in ICU admission should be captured in the economic analysis. The substantial costs are associated with the ICU stay itself and, as highlighted by Experts feedback, the prolonged inpatient rehabilitation period following the treatment of ICANS events with high-dose steroids.<br><br>Whilst the revised base case captures the ICU costs, it does not capture the impact on patient HRQoL, or the broader substantial impacts that reduced ICU admissions can have on overall NHS capacity. These uncaptured benefits are discussed in **Issue 3**.<br><br>***Application within the revised base case***<br><br>The economic model has been updated to include the ICU costs for all 2L and 3L treatments. Comparative data for ICU admissions between liso-cel and axi-cel 3L in the UK are not available. Instead, the model uses comparative data in the 2L setting from a recent French real-world evidence (RWE) study. This French RWE study is a retrospective cohort study of adult patients treated with CAR T in France between January 1, 2018, and December 31, 2023, identified through the French national hospital discharge databases ("Programme de Médicalisation des Systèmes d'Information" or PMSI), which is an exhaustive database for all hospitalisations in France. A total of 380 patients with axi-cel 2L (n=[redacted]) or liso-cel (n=[redacted]) infusion were included.[2]<br><br><u>Proportion of patients requiring ICU admissions</u><br><br>Results from this study reported that ICU admission was required in [redacted] of patients receiving liso-cel and [redacted] of patients receiving axi-cel.[2] This data reflects the comments made by Clinical Experts during ACM1, who noted that liso-cel would "reduce resource use, including length of hospital stay and intensive care use" when compared with axi-cel |

(NICE Draft Guidance, para 3.4). As the only data source capturing resource use associated with both liso-cel and axi-cel 2L, the French RWE study is invaluable and complements the TRANSFORM trial, for which only data for liso-cel can be derived.[2] For completeness, a scenario analysis has been presented using ICU admission rates from TRANSFORM ([redacted]%) for liso-cel and ZUMA-7 (25.0%) for axi-cel. These data suggest the comparative benefit of liso-cel versus axi-cel from the French RWE study may be conservative. Nonetheless, the French RWE study was considered more robust and thus used for the revised base case given the differences in populations and trial designs between TRANSFORM and ZUMA-7.[3, 4] A UK RWE study supported the fact that axi-cel results in a significant number of ICU admissions and 3L axi-cel leads to more ICU admissions (20%) than 2L axi-cel ([redacted] from the French RWE study).[5] Although this data was not incorporated into the economic analysis to maintain consistency of sources, it further underscores the conservative nature of the revised base case and suggests that liso-cel may possess a superior safety profile.

For 2L SOC, the proportion of patients modelled to require ICU admission was [redacted]%, based on TRANSFORM. For 3L treatment, the proportion of patients modelled to require ICU admission was different for each treatment option and was informed by TRANSFORM for autoSCT ([redacted][3], Taheri *et. al.* (2019)[6] for alloSCT ([redacted]%; calculated value based on TRANSFORM) and Clinical Experts opinion sought for chemotherapy (2.75%). Radiotherapy was assumed to not be associated with any ICU admission.

Length of ICU stay

It was assumed there would be no difference in ICU length of stay (LOS) between liso-cel and axi-cel 3L, which can be interpreted as conservative approach as the median LOS for ICU was shorter for liso-cel ([redacted]) based on TRANSFORM compared with axi-cel 2L (5 days) based on ZUMA-7. The clinical trial estimates were not considered as the previous approach of using 4 days in TA895 for 2L axi-cel was criticised by the EAG for being too short. The average LOS for ICU stay was assumed to be 7.5 days, based on the median of 7–8 days estimated by Clinical Experts during technical engagement in TA872 for 3L axi-cel. This matches the LOS from TRANSFORM for SOC. The TA872 LOS was preferred over the French RWE LOS (of 5.7 days for liso-cel and axi-cel 2L) because it was considered to be more in line with NHS clinical practice. As such, 7.5 days based on the Clinical Experts' opinion was considered more appropriate.

The ICU cost per day is provided in Table 2 below, with a summary of the proportion of patients requiring ICU stay and the average length of ICU stay provided in Table 3.

**Table 2: Resource use costs for ICU admission**

| Input | Unit cost | Source |
|---|---|---|
| ICU cost per day | £5,032 | NHS Reference Costs 21/22. Weighted average of SA31(A to F), per day cost based on mean LOS from 17/18 schedule |

**Abbreviations:** ICU: intensive care unit; LOS: length of stay; NHS: National Health Service.

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Source: NHS Reference Costs 2021/22.[7]

**Table 3: Proportion of patients requiring ICU admission and length of ICU stay**

| Input | Value | Source |
|---|---|---|
| **Length of stay** | | |
| Liso-cel 2L | 7.5 days | Assumed equal to axi-cel median 7-8 days in ICU informed by Clinical Expert opinion during technical engagement p. 618 of Committee Papers (TA872) |
| Axi-cel 3L | | |
| SOC 2L/3L | | |
| **Proportion of patients requiring ICU stay (base case)** | | |
| Liso-cel 2L | [redacted] | French RWE (n=[redacted]) |
| SOC 2L | [redacted] | TRANSFORM CSR, Table 14.3.5.10.1 Hospital Resource Utilization (HRU) Result Safety Analysis Set |
| 3L treatments | | |
| Axi-cel | [redacted] | French RWE (n=[redacted]) |
| AutoSCT | [redacted] | TRANSFORM CSR, Table 14.3.5.10.1 Hospital Resource Utilization (HRU) Result Safety Analysis Set |
| AlloSCT | [redacted] | Taheri *et al.* (2019), which reported ICU rates for allogenic SCT were 2.75x higher than autologous SCT; Calculated value derived from TRANSFORM CSR |
| Radiotherapy | 0% | Assumption |
| Chemotherapy (3L only) | 2.75% | Clinical Expert opinion sought, November 2024 |
| **Proportion of patients requiring ICU stay (scenario analysis)** | | |
| Liso-cel 2L | [redacted] | TRANSFORM CSR Table 14.3.5.10.1 Hospital Resource Utilisation (HCRU) Results |
| SOC 2L | same as base case | |
| 3L treatments | | |
| Axi-cel | 25.0% | ZUMA-7 |
| AutoSCT | same as base case | |
| AlloSCT | | |
| Radiotherapy | | |
| Chemotherapy (3L only) | | |

**Abbreviations:** 2L/3L: second-line/ third-line; axi-cel: axicabtagene autoleucel; CSR: clinical study report; HCRU: healthcare resource utilisation; ICU: intensive care unit; liso-cel: lisocabtagene maraleucel; PMSI:

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French hospital discharge database; SOC: standard of care.
**Source:** TRANSFORM CSR (23 Oct 2023 DCO); French RWE (PMSI); NICE TA872.[2, 3, 8]

Using the inputs outlined above, the total ICU costs are summarised in Table 4. These costs were added as a weighted average to the proportion of patients receiving each treatment in each arm.

**Table 4: Total ICU costs included in the revised base for each treatment**

| Treatment | ICU cost for each treatment |
|---|---|
| **2L** | |
| Liso-cel | [redacted] |
| SOC | [redacted] |
| **3L** | |
| Axi-cel | [redacted] |
| Auto HSCT | [redacted] |
| Allo HSCT | [redacted] |
| Chemotherapy | £189 |
| Radiotherapy | £0 |

**Abbreviations:** HSCT: Hematopoietic stem cell transplantation; ICU: intensive care unit, SOC: standard of care.

***Revised base case results, incorporating the ICU costs***

Table 5 presents the revised base case results for liso-cel (with PAS) versus SOC including ICU costs. A scenario analysis has been conducted to show the impact of using TRANSFORM and ZUMA-7 data, which improves the ICER by around [redacted] versus the revised base case. Another scenario analysis excluding the ICU costs has also been conducted, it shows a cost saving for ICU costs of [redacted] for every patient treated with liso-cel versus axi-cel 3L.

**Table 5: Revised base case for liso-cel (with PAS) versus SOC, including ICU costs**

| | Incr. costs | Incr. QALYs | ICER | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|
| **Revised base case:** Addition of ICU costs using French RWE study | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Addition of ICU costs using TRANSFORM and ZUMA-7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Impact of **excluding ICU costs** from the revised base case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS:

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<table>
<tr><td></td><td>patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.</td></tr>
<tr><td>Issue 2: Inclusion of 3L AEs</td><td>
Given the high costs associated with AEs management, BMS consider it most appropriate for the revised base case to include the costs of AEs for all 2L and 3L treatments<br><br>
In the original base case, the CAR T tariff was assumed to capture all costs associated with the management of AEs up to 100 days after infusion. As such, the costs associated with the management of AEs were applied as follows:<br>
• 2L: via the CAR T tariff for liso-cel; costed granularly for SOC<br>
• 3L: via the CAR T tariff for axi-cel; not applied for other 3L therapies<br><br>
BMS acknowledge the Committee's preferred approach was to remove AE costs from the CAR T tariff applied for axi-cel 3L to ensure consistency with the original approach to not model AE costs for other non-CAR T 3L therapies. However, BMS consider it most appropriate to be consistent in its application of the CAR T tariff in the revised base case (i.e., without any adjustment) meaning that AE costs for 3L axi-cel are retained. Consequently, AE costs associated with all other non-CAR T 3L therapies have been added. This approach also ensures that all relevant differences in costs between the two model arms are captured, in line with the NICE reference case. Including AE costs in the 3L setting ensures a more accurate and comprehensive evaluation of treatments, where such costs are expected to be incurred in the clinical setting.<br><br>
The AE costs associated with each non-CAR T 3L therapy (ASCT, allo-SCT, chemotherapy and radiotherapy) were assumed to be the same as the AE costs for 2L SOC (£7,310). This cost was then applied for the proportion of patients receiving a non-CAR T 3L therapy, as shown in Table 6.<br><br>
Table 6: Subsequent therapies (3L) AE costs adopted in the revised base case
<table>
<tr><th rowspan="2">Subsequent treatment</th><th colspan="2">Liso-cel</th><th colspan="2">SOC</th></tr>
<tr><th>Proportion[a]</th><th>AE cost applied[b]</th><th>Proportion[a]</th><th>AE cost applied[b]</th></tr>
<tr><td>Proportion of patients who receive a subsequent treatment</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>ASCT</td><td>[redacted]</td><td>£7,310</td><td>[redacted]</td><td>£7,310</td></tr>
<tr><td>Allo-SCT</td><td>[redacted]</td><td>£7,310</td><td>[redacted]</td><td>£7,310</td></tr>
<tr><td>3L+ chemotherapy</td><td>[redacted]</td><td>£7,310</td><td>[redacted]</td><td>£7,310</td></tr>
<tr><td>3L+ radiotherapy</td><td>[redacted]</td><td>£7,310</td><td>[redacted]</td><td>£7,310</td></tr>
<tr><td>3L+ CAR T</td><td>[redacted]</td><td>Considered included within the CAR T tariff</td><td>[redacted]</td><td>Considered included within the CAR T tariff</td></tr>
</table>
</td></tr>
</table>

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**Notes:** [a]The % of patients receiving each subsequent treatment may sum to over 100% as patients may receive more than one subsequent treatment. [b]The AE cost applied for all non CAR T subsequent therapies was assumed to be £7,310, based on the total cost of AEs modelled for 2L SOC.
**Abbreviations:** 3L+: third-line and beyond; Allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; SOC: standard of care.
**Source:** NICE Draft Guidance, BMS Data on File: TRANSFORM CSR (final DCO; October 2023).[3]

Results of the revised base case for liso-cel (with PAS) versus SOC that include the AE costs for all 3L subsequent therapies are presented in Table 7. A scenario analysis has been conducted to show the substantial impact of not including these 3L AE costs. This scenario follows a similar approach to the Committee's preferred assumption, that is, it excludes all AEs costs which includes removing those for axi-cel 3L from the CAR T tariff. However, following confirmation from NHS England that ICU costs are not included in the CAR T tariff, it was noted that the AEs costs removed for axi-cel 3L also included ICU costs and would lead to overestimated AE costs removed from the comparator arm (based on the original model). Thus, a correction was made in the revised model to adjust for this (in the revised model, the correction is reflected in the option to choose the tariff labelled as "Use tariff with AE costs (excluding ICU costs associated with AEs) removed (Corrected Committee base case)").

Detail on the AE costs calculations can be found in **Appendix 3.**

**Table 7: Cost-effectiveness results for liso-cel (with PAS) versus SOC when accounting for AE costs for all 3L therapies**

| | Incr. costs | Incr. QALYs | ICER | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|
| **Revised base case:** Inclusion of AE costs for all 3L therapies | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Impact of **excluding AE costs for all 3L therapies** from the revised base case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

**Issue 3: Uncaptured benefits**

**The use of the CAR T tariff means there are additional benefits associated with liso-cel that will result in cost-savings for the NHS that cannot be captured in the revised base case**

The CAR T tariff apply to all CAR T therapies and includes costs associated with leukapheresis, CAR T therapy delivery in hospital, AEs in hospital (excluding ICU costs), monitoring for 100 days and training. This means that costs related to the administration of both liso-cel and axi-cel 3L are required to be modelled using the same NHS CAR T tariff cost of £58,964. This tariff is based on real-world CAR T patients treated in 2022/23. Although the tariff has been updated and inflated to reflect 2024/25 costs, it is not based on liso-cel. This means the tariff currently predominantly reflects the costs associated with

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| | axi-cel 3L, which have a less favourable safety profile than liso-cel. Although the tariff is unlikely to be revised immediately, should liso-cel receive a positive NICE recommendation, it could be revised downwards in future, when the more favourable safety profile of liso-cel has been observed in clinical practice. In this scenario, the updated tariff will be calculated on a cohort of patients treated with axi-cel and liso-cel (as tisa-cel is no longer available) and, thus, will benefit from cost savings associated with liso-cel's more favourable safety profile.<br><br>As a result, the use of the CAR T tariff (of £58,964) means the additional benefits associated with liso-cel cannot be captured in the revised base case. These uncaptured benefits are directly linked to the more favourable safety profile of liso-cel compared to axi-cel 3L<br><br>• substantial differences in AE costs are expected between liso-cel and axi-cel 3L. In **Issue 3a**, BMS has quantified this cost-saving by adjusting the CAR T tariff.<br><br>• many patients are likely to receive liso-cel in an outpatient setting, reducing the costs associated with the delivery of liso-cel compared to axi-cel. In **Issue 3b,** BMS has quantified this cost-saving by adjusting the CAR T tariff.<br><br>• The combination of these two elements means that liso-cel is likely to alleviate significant capacity constraints within the NHS by reducing the requirement for both hospital beds, as well as ICU admission (**Issue 1**). This, combined with the improved patients HRQoL may have further reaching benefits that cannot be captured in the revised base case. In **Issue 3c**, BMS has described qualitatively how liso-cel can alleviate capacity and improved patients HRQoL.<br><br>Each of these issues are considered in more detail in the sub-issues below. |
| **Issue 3a: Liso-cel favourable safety profile can be captured by adjusting the CAR T tariff** | **Liso-cel has a more favourable safety profile compared with axi-cel 3L, particularly in relation to CRS and neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS)**<br><br>The key benefit of liso-cel compared with axi-cel is its improved safety profile. This was highlighted by the Clinical Experts at ACM for this appraisal when comparing with axi-cel the NICE draft guidance (para 3.4) states that "the clinical experts at the Committee meeting also noted that the key difference between liso-cel and axi-cel was the safety profile. There are expected to be substantially fewer grade 3 and 4 adverse events for people having treatment with liso-cel." Indeed, the Clinical Experts also unanimously agreed, based on the clinical trial evidence available for each therapy, that liso-cel has an improved safety profile compared to axi-cel 2L (i.e., fewer CRS and neurotoxicity events). This improved safety profile is also expected when comparing liso-cel with axi-cel 3L and therefore this difference should be captured, where possible, within the economic analysis.<br><br>For example, a naïve comparison of the incidence of AEs observed in at least 5% of |

patients between liso-cel and axi-cel 2L and 3L from the respective trials (TRANSFORM, October 2023 DCO; ZUMA-7, Westin et al. [2023]; ZUMA-1, Locke et al. [2019]) is presented in Table 8. The overall number of Grade ≥3 AEs is comparable in patients who received liso-cel compared with those who received axi-cel 2L and 3L.[3, 4] More importantly, more Grade 1 -2 CRS and neurotoxicity events and Grade ≥3 CRS events were observed in patients who received axi-cel 2L and 3L compared with those who received liso-cel.[3, 4] More Grade ≥3 neurotoxicity were observed in patients who received axi-cel 2L compared with those who received liso-cel. A full comparison of AEs between liso-cel and axi-cel has been provided in **Appendix 3.**

**Table 8: Naïve comparison of key Grade ≥3 AE and Grade 1–2 AEs of special interest occurring in ≥5% of patients between TRANSFORM (liso-cel), ZUMA-7 (2L axi-cel) and ZUMA-1 (3L axi-cel)**

| Category | Liso-cel from TRANSFORM* (N=92), n (%) (October 2023 DCO)[3] | Axi-cel 2L from ZUMA-7 (N=170), n (%) (Westin et al. 2023)[4] | Axi-cel 3L from ZUMA-1* (N=108), n (%) (Locke et al. 2013)[18] |
|---|---|---|---|
| **Grade ≥3 AEs** | | | |
| Overall | [redacted] | 91.0% | 98% |
| CRS | [redacted] | 6.5% | 4.6% |
| Neurotoxicity | [redacted] | 21.2% | 2.8% |
| **Grade 1–2 AEs** | | | |
| CRS | [redacted] | 85.9% | 88.0% |
| Neurotoxicity | [redacted] | 39.4% | 63.9% |

**Abbreviations:** 2L: second-line; AE: adverse event; CRS: cytokine release syndrome; DCO: data cut-off
*TRANSFORM and ZUMA-1 AE rates are used to adjust the CAR T tariff based on liso-cel safety profile

**The differences in safety profiles between liso-cel and axi-cel (3L) are not captured in the revised base case, because the same CAR T tariff of £58,964 is used for both treatments. This means that the revised base case is conservative, and fails to consider the important cost savings, that will result from the more favourable safety profile of liso-cel**

BMS have calculated the potential cost savings that would be expected with the management of AEs associated with liso-cel compared with axi-cel 3L by adjusting the CAR T tariff to reflect liso-cel AE profile. The AE profiles costed for liso-cel and axi-cel 3L were based on the incidence rates reported in TRANSFORM for liso-cel and ZUMA-1. The costs captured were AE management and rehabilitation costs required following ICU admission for neurotoxicity. Further details on the AEs cost calculation is provided in

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**Appendix 3.**

The total costs for AE management per patient associated with liso-cel and 3L axi-cel were calculated as £[redacted] and £20,483, respectively. This represents a cost saving due to AEs of £[redacted] for every patient treated with liso-cel versus axi-cel 3L. An illustrative scenario whereby the CAR T tariff has been adjusted to reflect his difference is provided in Table 9.

**Table 9: Scenario analysis results for liso-cel (with PAS) versus SOC when accounting for the differences in AE and rehabilitation costs between liso-cel and axi-cel 3L**

| | Incr. costs | Incr. QALYs | ICER | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|
| **Revised base case** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Revised base case, **but including the AE and rehabilitation cost adjustment** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

The improved safety profile of liso-cel would, therefore, be expected to translate to a large cost saving for the NHS. Due to the limitations with the application of the CAR T tariff, this benefit is excluded from the revised base case, but is nonetheless an important cost-saving associated with liso-cel that should be considered by the Committee.

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**Issue 3b Liso-cel's outpatient delivery can be captured by adjusting the CAR T tariff**

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**The favourable safety profile of liso-cel provides the potential for liso-cel to be delivered within an outpatient (ambulatory) setting, unlike existing CAR T therapies. Experts feedback strongly highlights the appetite of the clinical community to deliver liso-cel within the outpatient setting, which is likely to be associated with substantial cost-savings and a number of further uncaptured benefits**

Outpatient CAR T therapy delivery entails lymphodepletion therapy, CAR T infusion and subsequent follow-ups within an outpatient setting, with inpatient admission only for the management of AEs as required.

Overwhelming support for outpatient delivery of liso-cel was gathered as part of the Clinical Experts Interviews (**see Appendix 1)**.[1] The Experts feedback highlighted that they would expect to be able to deliver liso-cel in the outpatient setting for 50 - 80% of patients.[1] In addition, results from a BMS CAR T insight report showed that [redacted] of the [redacted] CAR T sites plan to have outpatient delivery of CAR T should liso-cel become available.[9] Whilst the outpatient delivery of liso-cel would be dependent on a number of logistical factors, such as having the appropriate infrastructure, processes and staffing in place, Experts feedback highlighted that the most important clinical considerations relate to careful patient selection and the ability of patient and their carers to quickly identify CAR T

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| | specific AEs enabling the CAR T sites to promptly treat these AEs.[1] Given the favourable safety profile of liso-cel over axi-cel, Experts feedback was overwhelmingly in support of the full outpatient delivery of liso-cel, whilst clearly stating that this would not be something they would consider for axi-cel.[1]<br><br>The majority of clinicians contacted by BMS indicated that they would adopt outpatient delivery protocols within 3–12 months of liso-cel being available. This is because they would need time to get some experience in delivering liso-cel and to set up the appropriate infrastructure required for outpatient delivery.[1] However, one clinician, whose CAR T centre already has an outpatient infrastructure for other lymphoma treatments (bi-specific antibodies and ASCT), expressed interest in the immediate adoption of outpatient delivery from the first patient treated with liso-cel.<br><br>The outpatient delivery of liso-cel is expected to translate to benefits for hospitals, patients and their caregivers.<br><br>***Outpatient delivery of liso-cel would lead to reduced hospitalisation resource use and costs***<br><br>It is widely acknowledged that the costs and resource use associated with an inpatient stay far outweigh those associated with an outpatient visit. Indeed, the comparison of post-infusion monitoring related healthcare resource use cost for the inpatient and outpatient delivery of liso-cel based on TRANSFORM and PILOT (a phase 2 trial for patients treated with liso-cel for relapsed or refractory LBCL for whom stem cell transplant is not suitable), reported that the median 6-month post-infusion costs were 68% lower for outpatient compared with inpatient delivery of liso-cel in the 2L setting.[10] Moreover, costs associated with the use of healthcare facilities, in particular hospitalisation costs, were the largest contributor to overall median 6-month costs.[10]<br><br>The cost savings associated with the outpatient delivery of liso-cel should therefore not be underestimated. It is also anticipated that savings would increase as outpatient delivery capabilities continue to develop and become more efficient in the CAR T treatment centres. However, as the delivery costs of liso-cel are included within the CAR T tariff, the revised base case does not capture any of the cost-savings associated with outpatient delivery.<br><br>To illustrate this, two scenario analyses exploring the potential impact of outpatient delivery of liso-cel were conducted, in which 50% and 80% of patients were assumed to receive liso-cel in an outpatient setting. In these scenarios, the CAR T tariff has been adjusted to reflect the cost-savings associated with the outpatient delivery. Full details of these scenarios are provided in **Appendix 4**. The results of these scenario analyses showed that the cost savings resulting from outpatient delivery of liso-cel are expected to range between £[redacted] and £[redacted] per patient (Table 10).<br><br>**Table 10: Scenario analysis results for liso-cel (with PAS) versus SOC when** |

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**accounting for outpatient delivery**

| | Incr. costs | Incr. QALYs | ICER | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|
| **Revised base case** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Revised base case, **including outpatient delivery adjustment for 50% of liso-cel patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario analysis:** Revised base case, **including outpatient delivery adjustment for 80% of liso-cel patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; LYs: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

The outpatient delivery of liso-cel would be expected to translate to a large cost saving for NHS England. This benefit is not captured in the revised base case, but is nonetheless an important cost-saving associated with liso-cel that should be considered by the Committee.

In addition to cost-savings, Experts feedback indicated that the outpatient delivery of liso-cel would result in much improved HRQoL for patients **and release of bed and staffing capacity. This is further discussed in Issue 3C.**

**Issue 3C: Uncaptured benefits of increasing bed capacity and improving patients HRQoL**

**Increasing ICU and inpatient bed capacity**

**The favourable safety profile of liso-cel leads to reduced ICU admission rates over axi-cel. While the cost savings associated with this have been captured in the revised base case (Issue 1), increasing ICU capacity is likely to lead to further benefits that cannot be captured in the revised base case**

The strain on ICU is of particular importance in the UK. One analysis has shown that the UK had the 2nd lowest bed capacity (after Sweden) in 2021 compared with countries in the EU, as per the OECD database, despite increases in the number of beds.[11] The strain on ICU bed capacity in the UK is further exacerbated by a high adult critical care occupancy rate in England of 79.1%, as recorded by NHS England (NHS E) in October 2024.[12]

Feedback from two ICU clinicians experienced in the management of CAR T related toxicities (see **Appendix 2**) reported close to 100% ICU capacity at their hospital Trusts, which is significantly higher than the already overstretched ICU occupancy reported by NHS E. They emphasised the use of a CAR T, with a lower ICU admission rate will release ICU bed capacity, reducing healthcare costs, and enhance the overall efficiency and effectiveness of the healthcare system. The availability of more ICU beds would allow

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| | for better management of patient flow for other critically ill patients such as patients from A&E, surgery and other hospital wards. This would enable more timely admissions, improving their outcomes by reducing the severity of their conditions upon ICU entry. Timely ICU admissions are crucial for improving patient outcomes and prognosis, the data from the ICU National Audit tool (Intensive care national audit and research centre - ICNARC) also supports this This is particularly true for patients waiting for surgery for whom admission in ICU can potentially reduce their overall length of hospital stay.[13] Reducing ICU admissions for CAR T patients would also alleviate some of the burden on healthcare providers, help optimise resource utilisation within the NHS, and improve the overall patient experience and outcomes.[2]<br><br>**The outpatient delivery of liso-cel would increase inpatient bed capacity to deliver other treatments**<br><br>Experts feedback highlighted the extreme pressures that NHS services continue to face, particularly at CAR T centres, with delays in transplants, limited staff capacity in inpatient wards, and an increase in new treatments that require mandatory inpatient admission (such as admission for commencement of bispecific treatments, prolonged mandatory admission for gene therapy and clinical trials).[1,2] With its favourable safety profile, there is great potential for liso-cel to be delivered within the outpatient setting, relieving the burden on inpatient hospital capacity, enabling more patients to receive timely treatment, again improving overall patient experience and outcomes.<br><br>**Improving patients HRQoL**<br><br>**The reduced incidences of high-grade ICANS and ICU admissions associated with liso-cel will protect patients from the severe physical and psychological burden associated with ICU treatment, providing significant benefits to patient HRQoL**<br><br>Following an ICU stay for the treatment of ICANS and the use of high-dose steroids to treat the neurotoxicity, the Experts feedback highlighted that patients will require 2–3 weeks of inpatient rehabilitation to recover from the extreme effects on their neurological and physical condition.[1] This has frequently been sighted by the CAR T Experts as the most difficult part of treating patients with axi-cel for the patient, their families as well as the wider clinical teams. Post-ICU, the CAR T Experts feedback and ICU clinicians have reported patients may experience 'post-ICU syndrome'. They may be very depressed requiring support from psychologists, and the neurological effects can remain for some time. Experts feedback indicated that following an ICU stay for ICANS, some patients 'are not the same person again for a long time'. Their physical condition is also likely to have deteriorated, with muscle wastage from being in ICU exacerbated by the effects of high dose steroids and also intubation and ventilation. This results in the need for considerable physiotherapy and occupational therapy support. Many patients may also be malnourished, requiring naso-gastric or parenteral nutrition with dietitian support. Due to the significant psychological and physical impact of ICANS and ICU admission, described |

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| | by the ICU clinicians as 'post ICU syndrome, Experts feedback have highlighted the difficulty patients experience engaging with allied health professionals in their rehabilitation. The high-dose steroids and prolonged hospitalisation, also leads to an increased risk of infections, including hospital-acquired pneumonia further deteriorating the patients HRQoL. Finally, the impact of an ICU stay on caregivers of patients can be extremely distressing, with ICU clinicians noting that family members also experience a version of post-ICU syndrome called post-ICU syndrome-family, thereby demonstrating the manifold value of reduced ICU admission associated with liso-cel.[1,2]<br><br>**The outpatient delivery of liso-cel is also expected to improve patient HRQoL.**<br><br>In a CAR T patient and caregiver UK report by Stenson *et al.* (2023) and patient-caregiver experience of 2L CAR T research sponsored by BMS [14], patients described disruption to their lives and a loss of normality associated with receiving CAR T as an inpatient. They emphasised the negative impact of intensive monitoring in an inpatient setting and the physical constraints in the hospital.[14, 15] One patient even described feeling like a "caged animal", when citing the prolonged hospital admission and monitoring required.[15, 16] Some patients reported feelings of loneliness and isolation in both a physical and emotional capacity.[14] The Experts feedback were keen to point out that outpatient delivery of liso-cel was likely to benefit the patient the most. It would spare patients from the impact of being admitted to hospital, and its associated physical and emotional implications. Being able to go home, patients can be supported by family and friends, maintain their overall performance status, that naturally deteriorates when a patient is confined to a single room on CAR T or haematology wards, experience improved nutrition by eating their preferred food at home, and benefit from improved sleep by sleeping in their own bed. They are also at a reduced risk of hospital-acquired infections through minimising their length of hospital stay. The Experts feedback described how these benefits combined, along with the significant support from their friends and families as well as the hospital CAR T team can significantly improved the patients HRQoL. |

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**Summary**


While BMS accepts it is not possible to directly compare liso-cel to axi-cel 2L, this appraisal fails to capture the true benefit of liso-cel expected in clinical practice. In the revised base case submitted in this response, BMS has attempted to capture the benefit of liso-cel compared to routinely available axi-cel 3L. However, BMS is concerned that the CAR T tariff is leading to distorted analyses with significant uncaptured benefits causing the revised base case not to fully recognise the additional benefits of liso-cel's safety profile, which can improve patient outcomes and enhance NHS capacity.

Consequently, BMS urge the Committee to consider the uncaptured benefits of liso-cel in its decision-making. BMS has, where possible, quantified the potential cost savings of some of these uncaptured benefits by adjusting the CAR T tariff to reflect the reduced AE management (**Issue 3a**) and the outpatient delivery (**Issue 3b**). Other uncaptured benefits related to the NHS capacity release and improved HRQoL remain uncaptured (**Issue 3c**).

Table 11 presents the impact that some of these uncaptured benefits would have on the revised base case if captured quantitively in the model. In the scenario analysis including cost savings from both the reduced AE management and the outpatient delivery, there is almost a 100% increase in the cost-savings [redacted]) compared to the revised base case [redacted]). This significant difference highlights the major impact of the uncaptured benefits of liso-cel, which cannot be ignored. The more favorable safety profile of liso-cel not only reduces the burden of AE management but also enables outpatient delivery, leading to substantial cost savings and demonstrating the profound economic and clinical advantages of liso-cel over other treatments, which the committee should include in their decision making.


**Table 11: Scenarios analyses for liso-cel (with PAS) versus SOC including cost-savings associated with liso-cel safety profile and outpatient delivery**

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) | INHB at £20,000 | INHB at £30,000 |
|---|---|---|---|---|---|
| Revised Base case (BC) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Revised BC + Cost savings from reduced AE management (Issue 3a) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Revised BC + Cost savings from 50% outpatient delivery (Issue 3b) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Revised BC + Cost-savings from reduced AE management (3a) and 50% outpatient delivery (3b)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALYs: quality-

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| | adjusted life years. |

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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## Appendix 1

### Summary Report of the interviews held with nine clinical experts experienced in the delivery of CAR-T therapies from across England[1]

On the 14th of November 2024, NICE published a negative draft guidance for lisocabtagene maraleucel (liso-cel) for treating relapsed or refractory large B-cell lymphomas (LBCL) after first-line chemotherapy when a stem cell transplant (SCT) is suitable [ID3887].

As part of generating a response to the draft guidance, BMS sought input from clinical experts who deliver chimeric antigen receptor T cell (CAR T) therapy within NHS England on the following topics:

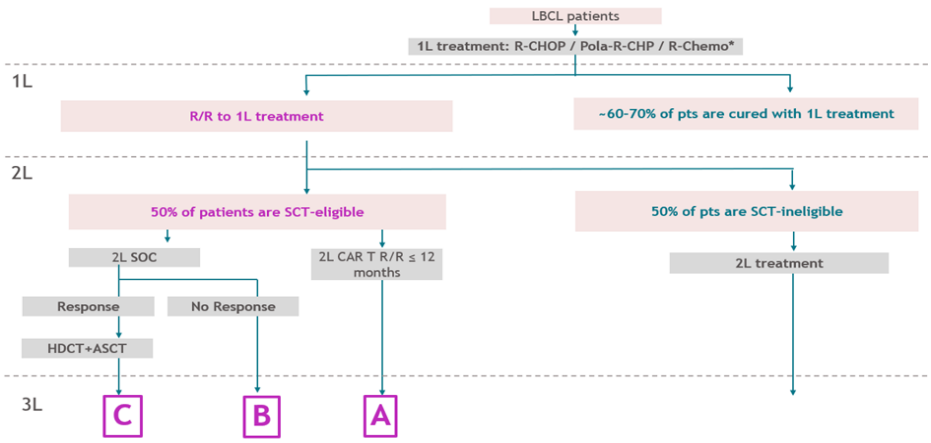
- Proportion of patients who are eligible to receive a 3rd line (3L) treatment after receiving either liso-cel or high-dose chemotherapy and SCT – standard of care (SoC) for LBCL
- Appetite and feasibility for delivering liso-cel in the outpatient setting
- Uncaptured benefits resulting from comparing second line (2L) liso-cel to high-dose chemotherapy and SCT and not 2L axi-cel.

BMS held individual virtual calls with nine CAR T clinical experts from different CAR T centres across England (including the North, Northwest, Midlands, London, South and Southwest regions) ranging from first wave CAR T centres to CAR T centres that are preparing to infuse their first patient. Full minutes of the clinician validation meetings have been provided as part of the reference pack attached with this response. The following is an executive summary of the discussions held with the clinical experts.

### Proportion of Patients who are Eligible to Receive a 3L treatment

**Appendix Figure 1** was presented during the meetings, and the clinical experts were asked to estimate what proportion of patients depicted in category A, B and C would receive 3L treatment in the current treatment landscape.

### Appendix Figure 1: LBCL patient flow




**Footnotes:** *CHOP like chemotherapy

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

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**Consultation on the draft guidance document – deadline for comments: 5pm on Thursday 5 December 2024. Please submit via NICE Docs.**

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

A summary of the clinical expert estimates for each category is presented in Appendix Table 1.

**Appendix Table 1: Clinical expert estimates for the proportion of patients receiving 3L treatment in each category depicted in Appendix Figure 1**

| Category | Clinical Expert Consensus on Proportion Moving to 3L Treatment |
|---|---|
| **A** (2L CAR T, Relapsed/Refractory within 12 months) | **70–95%** |
| **B** (Eligible for 2L SCT, Non-responsive to Reinduction) | **60–90%** |
| **C** (Received 2L ASCT) | **60–90%** |

**Abbreviations**: 2L/3L: second/third-line; CAR T: chimeric antigen receptor-T cell; ASCT: autologous stem cell transplant; SCT: stem cell transplant.

In Category A, which includes patients with disease that is refractory or has relapsed (R/R) within 12 months of first-line (1L) therapy receiving 2L CAR T therapy like liso-cel, 70–95% of these patients are expected to proceed to 3L treatment. The primary factors influencing the ability to treat these patients at 3L are fitness the aggressiveness of the disease with most patients remaining relatively fit post CAR -T. Minimal differences exist between liso-cel and axi-cel regarding progression to 3L, as treatment failure is typically driven by disease biology rather than toxicity.

Category B consists of patients eligible for 2L high-dose chemotherapy and SCT who are unresponsive to reinduction therapy. An estimated 60–90% of these patients are expected to proceed to 3L treatment. This high rate is attributed to the availability of well-tolerated 3L options like bispecific antibodies. However, some patients remain chemotherapy-refractory, making it impossible for them to continue treatment and would be treated with palliative intent.

For Category C, patients who received a SCT in 2L, 60–90% are anticipated to be fit enough to advance to 3L treatments. These patients typically experience less aggressive disease due to remission post-reinduction therapy. However, attrition of approximately 10–15% may occur between lines of therapy.

Generally, there was consensus from all CAR T clinical experts that the vast majority of patients in this indication (i.e. patients whose disease is refractory or relapsed within 12 months of 1L therapy who are eligible for high-dose chemotherapy and SCT at 2L) would receive a 3L treatment, irrespective of the 2L treatment received. This is due to patient fitness (they are SCT-eligible) and the availability of bispecifics at 3L which are considered to be well tolerated meaning that most patients would be fit enough to receive a 3L treatment.

### Potential for Liso-cel Delivery in the Ambulatory Setting

Regarding the potential for ambulatory delivery of liso-cel, it was clear from the CAR T clinical expert

feedback that the current ambulatory capacity differs between CAR T centres, with some centres already giving SCT and also lymphodepletion chemotherapy pre CAR T infusion in the ambulatory setting.

Current clinical practice

The CAR T clinical experts stated that SCT is mostly performed in ambulatory settings, with inpatient care provided as necessary for toxicity management. Lymphodepleting chemotherapy is also frequently administered via outpatient protocols. However, ambulatory care for SCT is not available at all centres currently. CAR T therapies such as axi-cel typically involve inpatient monitoring for 10–14 days post-infusion due to toxicity concerns, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

CAR T Ambulatory Pathway

None of the 9 consulted CAR T clinical experts offer a fully ambulatory delivery for axi-cel. However, the potential for delivering liso-cel in an ambulatory setting was unanimously supported by the 9 CAR T clinical experts consulted. A typical ambulatory pathway would involve outpatient lymphodepleting therapy followed by liso-cel infusion in a day-care or ambulatory care unit. Patients would then attend daily hospital visits for up to 14 days post-infusion. Some CAR T clinical experts recommend daily in-person reviews from Monday to Friday with telephone assessments over the weekend. This may reduce even further with more clinical experience with liso-cel toxicity and timing of adverse events. As is current practice, after day 10-14 discharge, patients would be reviewed to 2–3 times per week in the ambulatory setting. As more CAR T centres have now been commissioned, the vast majority of patients travel from home for clinical assessment during this early follow-up period. For patients residing more than 1–2 hours from a CAR T centre, accommodations in hospital-owned apartments or a hospital hotel will be provided, with a minority of CAR T sites using local hotels.

Advantages of Ambulatory Liso-cel

The ability to move liso-cel into the ambulatory setting is based on its improved toxicity profile compared to axi-cel, particularly in terms of reduced ICANS and CRS. This improved toxicity profile, in particular lower rates of grade ≥3 CRS and ICANS, resulting in fewer ICU admissions. Furthermore this will enable most patients to transition to outpatient care provided the appropriate infrastructure and caregiver support are available. Outpatient delivery will offer patients significant benefits, including enhanced quality of life, a reduced risk of hospital-acquired infections, faster recovery, improved mobility, and the comforts of home, which often results in better nutrition. Hospitals benefit from the release of inpatient capacity for other treatments, cost savings, reduced ICU reliance, and the ability to scale treatment for other therapies and research participation.

Estimates of adoption of Ambulatory delivery of Liso-cel

Adoption of ambulatory delivery of liso-cel is projected to be in the region of 50–80% of patients treated with liso-cel. The main considerations influencing the ability to administer liso-cel in the ambulatory setting are caregiver support, comorbidities, travel distance, and infrastructure readiness. Uptake is expected to be among younger, fitter patients initially, and will likely increase with greater experience and confidence in liso-cel' s safety profile. CAR T clinical experts estimate that liso-cel will be adopted into the ambulatory setting

within 3-12 months post-reimbursement for initial rollout, with gradual expansion over time. However, one site is planning on treating their first liso-cel patient in the ambulatory setting due to confidence in liso-cel's toxicity profile and their infrastructure readiness.

Infrastructure and Logistics

Infrastructure requirements include day-care units, robust protocols, and daily hospital visits for the first 14 days post-infusion. Existing CAR T centres can adapt for ambulatory care with some adjustments, such as SOP updates and dedicated day units, to facilitate the transition to ambulatory care. Eligibility criteria for patients to be treated as an outpatient include proximity to centres, caregiver availability, and performance status (0–1). Comprehensive education for patients and caregivers on symptom identification and reporting is essential. A minority of patients who live over 1-2 hours away from the CAR T centre will need to be provided with ambulatory accommodation – which already exists at the majority of CAR T sites for patients who are currently discharged on day 10-14 post axi-cel.

Key Challenges of Ambulatory CAR T delivery

The CAR T clinical experts stated the key challenges include building clinical confidence in managing liso-cel-related toxicities amongst the wider CAR T clinical team, this includes familiarity with the timing of onset of toxicities and level of toxicities associated with liso-cel. It is essential to ensure local readiness around infrastructure and logistics as well as patient and carer education on symptom reporting to minimise risks of delayed symptom recognition at home. It is also important to acknowledge there will be patient or caregiver reluctance due to anxiety or logistical burdens.

**Uncaptured Benefits of Liso-cel**

Improved safety profile of liso-cel versus axi-cel

Overall, there was clear consensus from the CAR T clinical experts that the key benefit of liso-cel over axi-cel is the more favourable safety profile. Liso-cel' s improved safety profile includes a significantly lower incidence of CRS and ICANS, specifically grade ≤3 CRS and ICANS. The CAR T clinical experts expressed feeling comfortable with the management of high grade CRS but unanimously voiced concerns around the impact and burden with management of high grade ICANS and the significant impact it has on patient physically and emotionally. People who experience ≤3 ICANS require ICU admission and treatment with high-dose steroids and wider multidisciplinary team involvement with ICU team, haematologists, neurologists and radiologists, which is very resource intensive. All CAR T clinical experts mentioned how this neurological toxicity has a significant negative impact of patient with neurocognitive decline as well as muscle wastage and increased risk of infections due to high-dose steroids. The muscle deterioration in particular can be very challenging and patients require significant support of allied healthcare professionals, including physiotherapists, occupational therapists, dietitians and psychologists, in the post ICU period to regain patients overall physical and psychological health to a sufficient level where they can be discharged from hospital. This prolonged admission for post ICU often equates to an additional 14-21 days stay with outlier admission days quoted from the CAR T clinical experts of 60, 89 and even 130 days for rehabilitation. One CAR T clinical expert reported how some patients post high grade ICANS 'never go back to normal; they are not the same personality for a relatively long period of time'. Due to the significantly lower incidence of high grade ICANS

seen with liso-cel, the CAR T clinical experts do not expect this level physical or emotional burden or of rehab needs for people receiving liso-cel and see it as a significant advantage of this treatment. Overall liso-cel is seen to have a reduced length of in-patient stay compared to axi-cel. The reduction in CRS and ICANS associated with liso-cel over axi-cel would therefore lead to large benefits for both patients and carers in NHS practice.

Operational Benefit and Reduced Inpatient Cost

Liso-cel also offers significant cost savings. The lower toxicity profile leads to reduced hospital burden, cost savings, and improved patient QoL. The significantly lower incidence of high grade CAR T specific toxicities such as CRS and ICANS reduce the high ICU costs. The shorter ICANS related ICU and steroid-related rehabilitation periods further lower costs, offers the hospital and NHS a significant cost saving. Operationally, liso-cel shorter overall length of stays, which frees up both ICU beds and inpatient beds for other patients and therapies and allows hospitals to use their resources more efficiently and increase patient throughput. This improved capacity enables the provision of other treatments, such as bispecifics, gene therapy, and CAR T clinical trials in haematology beds and access to ICU beds for both elective surgery and emergencies.

Patient Experience

The CAR T clinical experts were clear on how traumatic an ICU admission, especially for ICANS, is for patients. Many patients show signs of Post Traumatic Stress Disorder (PTSD) post ICU admission. From a patient perspective, the vast majority of people who receive liso-cel will not experience the significant toxicities and adverse events outlined above and therefore will have an enhances quality of life compared to axi-cel, enabling a faster return to daily activities and reducing physical and psychological burden of treatment. This shortened treatment timeline and reduced adverse events is thought to contribute to an overall improved QoL.

**Conclusion**

The CAR T clinical expert consultation findings emphasise liso-cel's advantages in safety, tolerability, efficiency, and scalability. The potential for expanded ambulatory delivery could revolutionise CAR T therapy by improving accessibility, reducing healthcare costs, alleviating bed capacity and enhancing patient outcomes. To fully realise these benefits, further investments in infrastructure, staff training, and patient education are necessary.

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## Appendix 2

**Summary of discussion with 2 Intensive Care Specialist and Anaesthetist at large CAR T sites in London.** These clinicians have treated people who have CAR T since it was first introduced into the NHS. Both clinicians have published extensively on CAR T patients in ICU.

**How Frequently do you see CAR T patients staying in ICU for extended periods?**

Extended duration of stay in ICU for haematology patients was traditionally driven by infection and sepsis, such as pneumonia requiring ventilation in patients with persistent neutropenia. These patients drove a longer median of length of stay in ICU and the mortality rate were very high at approximately 80%. They were also associated with high costs; however, this level of deterioration was relatively rare.

Patients who undergo CAR T-cell therapy can experience severe side effects that can also lead to extended stays in the ICU. When CAR T was first used in the NHS, all patients were mandated to be treated as an inpatient for 4 weeks post infusion. CAR T patients were admitted to ICU more readily for monitoring of Cytokine Release Syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). More recently, with greater experience and the earlier use of tocilizumab and steroids, patients are admitted to ICU mostly due to high-grade ICANS which is severe neurotoxicity specifically observed in patients undergoing CAR T-cell therapy.

**What is the impact of CAR T toxicities on patients and their families?**

The majority of patients admitted to the ICU have deteriorated Glasgow Coma Scale (GCS) associated with higher-grade ICANS, grade 3 and above. These patients often require intensive monitoring and, in severe cases, intubation. The need for intubation and prolonged ICU stays for these patients results in extended bed occupancy and longer recovery.

After discharge from ICU the recovery process is lengthy and arduous, the patient can continue to require further monitoring from outreach teams who liaise with the ICU and intensive care consultant on call. The impact of specifically ICANS, on patients and their families is profound and multifaceted, encompassing both physiological and psychological dimensions. This prolonged recovery period means that patients are often not the same as they were before the treatment, affecting their ability to function and perform daily activities. Patients can suffer from post-ICU syndrome. The term "post-ICU syndrome" is used in critical care to describe the range of issues patients face, including both physical rehabilitation and psychological challenges. This syndrome extends beyond the patient to what is termed "post-ICU syndrome-family," acknowledging the significant emotional and psychological toll on family members. It takes a considerable amount of time for patients with ICU syndrome to regain their former selves.

**What is impact of CAR T-cell therapies on ICU services?**

It is widely known that in the UK, the critical care capacity is lower that other European countries and therefore many NHS hospitals often find it very challenging to ‘juggle’ patients who are very unwell and require intensive care, a situation that has persisted even after the COVID-19 pandemic.[17] As a result, ICUs in the UK often operate at or above full capacity, with beds frequently being occupied by multiple patients in a single day. This bed occupancy issue is a significant concern for ICU clinicians across the UK, as it impacts

the overall efficiency and capacity of critical care services.

The prolonged ICU stays and the need for one-to-one nursing care for patients with severe ICANS further complicates the situation and the impact on ICU capacity is notable. These patients require intensive and specialised care, which can limit the availability of ICU beds for other critically ill patients. Even patients who do not require intubation still occupy high-dependency unit (HDU) or ICU beds. The expansion of CAR T-cell therapy for various types of cancers and other diseases have led to an increased number of patients receiving this treatment. Although advancements in managing the toxicities associated with CAR T-cell therapy have reduced the severity and frequency of these adverse effects, the overall number of patients requiring ICU care remains a concern. Even if a smaller percentage of patients develop severe ICANS, the absolute number of patients needing ICU care can still be substantial due to the expanding pool of CAR T-cell therapy recipients.

**What would be the impact of a reduction in ICU requirement for patients receiving CAR T-cell therapy?**

There are current challenges associated with timely ICU admissions for patients seen by outreach teams in hospital wards or Accident & Emergency (A&E). Delays in securing ICU beds are a significant issue in clinical practice and can lead to patients becoming sicker, requiring longer ICU stays, and potentially worse outcomes. These delays are often due to the high demand for ICU beds, which are frequently occupied by patients requiring intensive monitoring and care. While CAR T-cell therapy patients contribute to this problem, they are certainly not the sole cause. Releasing ICU capacity will allow more patients who require ICU admission access to the appropriate level of care, which is currently not always the case. This issue was highlighted in the 5th Perioperative Quality Improvement Programme (PQIP) 2023-2024 report, which showed that more than half of patients with a ≥5% 30-day mortality risk, are not admitted to critical care.[14]

If a CAR T therapy were to become available that required fewer ICU admissions, the impact on the NHS would be highly beneficial and would alleviate some of the pressure on ICU resources. The availability of ICU beds would increase, allowing for better management of patient flow for other critically ill patients such as patients from A&E, surgery and other hospital wards. This would enable more timely admissions, improving their outcomes by reducing the severity of their conditions upon ICU entry. The data from the ICU National Audit tool (Intensive care national audit and research centre - ICNARC) also supports that timely ICU admissions are crucial for patient outcomes.[17]

**Who else would benefit from the reduction of CAR T patients needing to go to ICU?**

Healthcare providers and ICU clinicians would also benefit from this reduction. The availability of more ICU beds would alleviate the pressure on ICU staff, including specialised nursing staff and medical equipment which could then be allocated to other patients in need, allowing them to manage patient care more effectively and efficiently. This would reduce the strain on resources and improve the overall workflow within the ICU, leading to better patient management and care delivery.

Therefore, a CAR T therapy that minimises the need for ICU care would significantly benefit the NHS by optimising resource utilisation, improving patient outcomes, and enhancing the overall capacity and efficiency of critical care services.

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It was also noted that the ability to deliver CAR T in the outpatient setting would be a significant advantage for the NHS but particularly for patients who often find it very difficult to be in hospital for extended periods of time. This can impact their emotional and physical wellbeing and they would benefit from being treated via an ambulatory service.

**Summary**

The introduction of a CAR T-cell therapy with reduced ICU requirements would have a profound and far-reaching impact on the NHS. It would improve the timeliness and quality of care for all patients requiring ICU services, reduce healthcare costs, and enhance the overall efficiency and effectiveness of the healthcare system. The medium to long-term impact of neurotoxicities like ICANS on patients and their families is significant, involving extended recovery periods and substantial healthcare resource utilisation. The strain on ICU capacity due to prolonged bed occupancy and the need for specialised care for these patients underscores the importance of effective management strategies and resource allocation to ensure optimal patient outcomes and maintain the functionality of critical care services.

The systemic challenges of delayed ICU admissions and their impact on patient outcomes is supported by national audit data. Timely ICU admissions are crucial for improving patient prognosis, and the reduction in ICU requirements for CAR T-cell therapy patients would alleviate some of the burden on healthcare providers, help optimise resource utilisation within the NHS, and improve the overall patient experience and outcomes. This holistic approach to healthcare management aims to benefit the entire population by ensuring more efficient and effective use of critical care resources.

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## Appendix 3

The AE profiles of liso-cel and 3L axi-cel were granularly costed based on the incidence rates reported in TRANSFORM and ZUMA-1, respectively. The 3L trial of axi-cel was used based on the assumption that the 3L axi-cel AE profile was more representative of CAR T AE profiles currently used in UK clinical practice (see **Issue 3**).

The costs captured included costs for AE management based on NHS reference costs, ward stay for CAR T specific AEs (i.e. CRS and neurotoxicity Grade 1 – 2), treatment costs and additional rehabilitation costs associated with Grade ≥3 neurotoxicity after ICU admission.

### AE rates

A comparison of the Grade ≥3 AE and Grade 1–2 AEs of special interest occurring in ≥5% of patients between TRANSFORM (2L liso-cel), ZUMA-7 (2L axi-cel) and ZUMA-1 (3L axi-cel) has been presented in Table 12.

**Table 12: Comparison of Grade ≥3 AE and Grade 1–2 AEs of special interest occurring in ≥5% of patients between TRANSFORM (2L liso-cel), ZUMA-7 (2L axi-cel) and ZUMA-1 (3L axi-cel)**

| Category | Liso-cel (n=92), n (%) | Axi-cel from ZUMA-7 (N=170), n (%) | Axi-cel from ZUMA-1 (N=108), n (%) |
|---|---|---|---|
| **Grade ≥3 AEs** | | | |
| Cytokine release syndrome | [redacted] | 6.5% | 4.6% |
| Neurotoxicity | [redacted] | 21.2% | 2.8% |
| Neutropenia | [redacted] | 69.4% | 38.9% |
| Thrombocytopenia | [redacted] | 14.7% | 24.1% |
| Anaemia | [redacted] | 30.0% | 45.4% |
| Lymphopenia | [redacted] | 0.0% | 7.4% |
| Febrile neutropenia | [redacted] | 0.0% | 32.4% |
| Leukopenia | [redacted] | 29.4% | 16.7% |
| Prolonged cytopenia | [redacted] | 32.9% | 29.6% |
| Hypophosphatemia | [redacted] | 18.2% | 18.5% |
| Infections | [redacted] | 16.5% | 19.4% |
| Hypotension | [redacted] | 11.2% | 13.9% |
| Fatigue | [redacted] | 6.5% | 0.0% |
| Pyrexia | [redacted] | 8.8% | 13.9% |
| Hypokalaemia | [redacted] | 5.9% | 0.0% |
| Hypertension | [redacted] | 0.0% | 7.4% |
| Hypoxia | [redacted] | 9.4% | 11.1% |
| Diarrhoea | [redacted] | 0.0% | 4.6% |

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| | | | |
|---|---|---|---|
| Hypocalcaemia | [redacted] | 0.0% | 6.5% |
| Encephalopathy | [redacted] | 0.0% | 23.1% |
| Hyponatraemia | [redacted] | 0.0% | 11.1% |
| Neutrophil count decreased | [redacted] | 0.0% | 32.4% |
| White blood cell count decreased | [redacted] | 0.0% | 28.7% |
| Platelet count decreased | [redacted] | 0.0% | 15.7% |
| Confusional state | [redacted] | 0.0% | 9.3% |
| Alanine aminotransferase increased | [redacted] | 0.0% | 5.6% |
| Lymphocyte count decreased | [redacted] | 0.0% | 20.4% |
| Aphasia | [redacted] | 0.0% | 7.4% |
| Aspartate aminotransferase increased | [redacted] | 0.0% | 6.5% |
| Somnolence | [redacted] | 0.0% | 8.3% |
| **Grade 1–2 AEs** | | | |
| Cytokine release syndrome | [redacted] | 85.9% | 88.0% |
| Neurotoxicity | [redacted] | 39.4% | 63.9% |

**Sources:** TRANSFORM CSR (23 Oct 2023 DCO), Westin *et al.* 2023 and Locke *et al.* 2018.[3, 4, 18]

### AE costs

The costs associated with the management of AEs are presented in The costs associated with ICU stay for CRS and neurotoxicity Grade ≥3 are not presented here because they are presented in **Issue 1.**

**Table 13**, which have been updated since the original company submission to more appropriate NHS reference costs codes. While this does not impact the liso-cel arm (as the CAR T tariff is assumed to capture the AE costs), the AE costs associated with SOC have been updated in the base case in line with the costs reported below.

The costs associated with ICU stay for CRS and neurotoxicity Grade ≥3 are not presented here because they are presented in **Issue 1**.

**Table 13: Costs included with the model for the management of AEs that occurred in ≥ 5% of patients**

| AE | AE cost | Source |
|---|---|---|
| CRS (Grade ⩾3) | £837 (tocilizumab and dexamethasone) | The pack cost of tocilizumab 200 mg was sourced from the BNF and the pack cost of dexamethasone 33 mg was sourced from eMIT. The total dose for tocilizumab was 652 mg and the total dose for dexamethasone was 30 mg for the treatment of CRS (Grade 1–2).<br>The cost for additional healthcare resource use is assumed to be captured in ICU stay costs (see **Issue 3**) |
| CRS (Grade 1–2) | £842 (tocilizumab and | The pack cost of tocilizumab 200 mg was sourced from the BNF and the pack cost of dexamethasone 33 mg was sourced from eMIT. The total |

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| | | |
|---|---|---|
| | dexamethasone) + £5,622 (other healthcare resource use) | dose for tocilizumab was 652 mg and the total dose for dexamethasone was 90 mg for the treatment of CRS (Grade 1–2).<br>The cost for additional healthcare resource use is assumed equal to the cost of febrile neutropenia (Grade ⩾3). |
| Neurotoxicity (Grade ⩾3) | £5 (dexamethasone) + £9,949.52 (rehabilitation) | The pack cost of dexamethasone 33 mg was sourced from eMIT and the total dose was 60 mg.<br>Although CRS (Grade 3+) ICU days are captured externally from these costs, rehabilitation days are not and therefore 2 weeks of rehabilitation costs are included, based on 14 days of based on the cost for a complex specialised rehabilitation services level 1 (VC12Z), priced at £710.68 per day, reported in the NHS Reference Costs 21/22. |
| Neurotoxicity (Grade 1–2) | £12 (dexamethasone) + £5,622 (other healthcare resource use) | The pack cost of dexamethasone 33 mg was sourced from eMIT and the total dose was 135 mg.<br>The cost for additional healthcare resource use is assumed equal to the cost of febrile neutropenia (Grade ⩾3). |
| **Neutropenia** | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G). |
| Thrombocytopenia | £2,163 | NHS Reference Costs 2021/22: Weighted average of SA12(G-K) Thrombocytopenia |
| **Anaemia** | £2,801 | NHS Reference Costs 2021/22: Weighted average of SA03G-SA03H Haemolytic Anaemia, based on precedent in TA895 |
| Lymphopenia | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08G-J, based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **Febrile neutropenia** | £5,622 | NHS Reference Costs 2021/22: Weighted average of WJ07A and WJ07B, Fever of Unknown Origin with Interventions |
| Leukopenia | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **Prolonged cytopenia** | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **Hypophosphatemia** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| Infections | £1,943 | NHS Reference Costs 2021/22: Weighted average of WJ03 (A-G) Standard Infectious Diseases |
| **Hypotension** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Fatigue** | £0 | Assumption |
| Pyrexia | £1,307 | NHS Reference Costs 2021/22: Weighted average of WJ07 (A-D) Fever of Unknown Origin |

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| | | |
|---|---|---|
| Hypokalaemia | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Hypertension** | £781 | NHS Reference Costs 2021/22: Weighted average of EB04Z, Hypertension |
| Hypoxia | £2,707 | NHS Reference Costs 2021/22: Weighted average of DZ27 (M-U) Respiratory Failure |
| **Diarrhoea** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| Hypocalcaemia | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Encephalopathy** | £3,534 | NHS Reference Costs 2021/22: Weighted average of AA22 (C-G) Cerebrovascular Accident, Nervous System Infections or Encephalopathy, aligned with TA895 |
| **Hyponatraemia** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Neutrophil count decreased** | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **White blood cell count decreased** | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **Platelet count decreased** | £2,163 | NHS Reference Costs 2021/22: Weighted average of SA12(G-K) Thrombocytopenia |
| **Confusional state** | £3,534 | NHS Reference Costs 2021/22: Weighted average of AA22 (C-G) Cerebrovascular Accident, Nervous System Infections or Encephalopathy |
| **Alanine aminotransferase increased** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Lymphocyte count decreased** | £1,773 | NHS Reference Costs 2021/22 Other Haematological or Splenic Disorder SA08 G-J), based on precedent in TA895 (TA895 only used SA08G), assumed equal to neutropenia |
| **Aphasia** | £3,534 | NHS Reference Costs 2021/22: Weighted average of AA22 (C-G) Cerebrovascular Accident, Nervous System Infections or Encephalopathy, aligned with TA895 |
| **Aspartate aminotransferase increased** | £1,832 | NHS Reference Costs 2021/22: Weighted average of KC05 (G-N) Fluid or Electrolyte Disorders |
| **Somnolence** | £3,543 | NHS Reference Costs 2021/22: Weighted average of AA22 (C-G) Cerebrovascular Accident, Nervous System Infections or Encephalopathy, aligned with TA895 |

**Footnotes: Bold** indicates AE cost has been updated with this response.
**Abbreviations:** AE: adverse event; DCO: data cut-off; NHS: National Health Service; SOC: standard of care.
**Source:** NHS Reference Costs 2021/22.[7]

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

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## Appendix 4

### Calculation of outpatient and inpatient costs

To calculate the cost-savings associated with the outpatient delivery of liso-cel, the cost of administration for liso-cel and axi-cel 3L were calculated granularly.

Axi-cel was assumed to be associated with 14 days of inpatient monitoring followed by 14 days of outpatient monitoring for 100% of patients. The experts feedback suggested the majority of patients currently receiving axi-cel in clinical practice will be monitored as outpatients from day 15 after CAR T infusion until day 28.[1] During the 14 day outpatient period it was assumed, again based on experts feedback, that patients would require an outpatient visit 3 times a week (i.e. a total of 6 outpatient visits).[1] Although there are differences between CAR T centres across the UK, this approach was taken as it was considered to represent the consensus.

Experts feedback stated that 50–80% of patients would receive liso-cel as an outpatient. Therefore, two scenarios have been conducted, where 50% and 80% of patients are costed to receive 28 days of outpatient monitoring.[1] For these patients, [redacted]% were modelled to never transition to the inpatient setting due to AEs (as per TRANSFORM) and thus outpatient monitoring costs were assumed to apply daily up to day 14 and then 3 times a week from day 15 to day 28 (i.e. a total of 20 outpatient visits). The remaining [redacted]% of patients who did require inpatient visits following liso-cel infusion, they were modelled to transition to inpatients [redacted] days after infusion and remain as inpatients for a further [redacted] days, based on the median time to hospitalisation and median hospitalisation duration reported from TRANSFORM, and transition back to outpatient care thereafter up to 28 days (i.e. a total of [redacted] outpatient visits).

For the remaining patients who initially receive liso-cel in the inpatient setting were modelled to receive inpatient costs for [redacted] days, and then outpatient costs 3 times a week from day [redacted] to day 28.[1] The shorter length of stay as an inpatient with liso-cel ([redacted] days) versus axi-cel (14 days) was based on the mean LOS from the French RWE, which indicated that due to the favourable safety profile associated with liso-cel patients would move earlier to the outpatient setting. This was also validated by experts opinion.[1]

The cost per day for an inpatient and outpatient administration of CAR T are provided in Table 14 and a summary of the total inpatient and outpatient days modelled for liso-cel and axi-cel are provided in Table 15.

**Table 14: Resource use costs for CAR T administration**

| Resource use | Unit cost | Source |
|---|---|---|
| Outpatient visit | £144.99 | NHS Reference Costs 21/22. WF02A: Medical Oncology Service, Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up - Non Consultant Led |
| Inpatient days | £966.57 | NHS Reference Costs 2021/22: Weighted average of SA31(A to F) Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's [Elective] |

**Abbreviations:** CAR T: chimeric antigen receptor-T cell; NHS: National Health Service.
**Source:** NHS Reference Costs 2021/22.[7]

**Table 15: Breakdown of inpatient and outpatient administration costs for CAR T therapies**

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| Initial infusion setting | Percentage of patients | Transition | Outpatient visits | Inpatient visits | Total administration cost | Total administration cost (weighted average of outpatient/inpatient) |
|---|---|---|---|---|---|---|
| **Liso-cel – 50% outpatient** | | | | | | |
| Outpatient | Assumed 50% | [redacted] stay outpatient | 20.0 | 0 | [redacted] | [redacted] |
| | | [redacted] transition to inpatient | [redacted] | [redacted] | | |
| Inpatient | Assumed 50% | 100% transition to outpatient | [redacted] | [redacted] | [redacted] | |
| **Liso-cel – 80% outpatient** | | | | | | |
| Outpatient | Assumed 80% | [redacted] stay outpatient | 20.0 | 0 | [redacted] | [redacted] |
| | | [redacted] transition to inpatient | [redacted] | [redacted] | | |
| Inpatient | Assumed 20% | 100% transition to outpatient | [redacted] | [redacted] | [redacted] | |
| **Axi-cel 3L** | | | | | | |
| Inpatient | 100% | 100% transition to outpatient | 6.0 | 14.0 | £14,401.88 | £14,401.88 |

**Abbreviations:** axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.
**Source:** BMS: Clinical Validation Calls (2024).[1]

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Blood Cancer UK |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Blood Cancer UK are disappointed and concerned by the negative draft guidance for the use of Lisocabtagene maraleucel (liso-cel) at the 2L for patients with LBCLs. We reiterate the following |

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| | |
|---|---|
| | key messages from our previous submission and would ask that these be reconsidered sufficiently before the final decision is reached:<br>• The aggressive nature of large B-cell lymphoma and the impact of its treatments can have significant effects on the mental and physical health and quality of life of both patients and their loved ones.<br>• Patients with primary refractory and early relapsed large B-cell lymphoma face unmet needs brought about by the need for effective treatment options in the second line.<br>• Lisocabtagene maraleucel provides an innovative option with a curative potential for those who otherwise face poorer outcomes with current available treatments.<br>• The benefits of providing an effective and transformative one-time treatment, like liso-cel, as early as in the second line should not be overlooked. It means more people can benefit from improved access and can offer more patients an opportunity of a cure and better quality of life as a result.<br>• Offering liso-cel at the second line could potentially spare many people from futile treatments and their associated toxicities whilst giving them their best chance at a cure earlier on in their treatment pathways. |
| 2 | The treatment pathway for LBCLs has changed rapidly in recent years and, from our discussions with clinicians, it has been made clear that Axicabtagene ciloleucel (axi-cel) is widely recognised as the current standard of care for those patients who relapse within 12 months of receiving first-line chemotherapy (and are fit for a ASCT) – making it the main alternative to liso-cel in clinical practice. While we recognise why NICE cannot define those treatments available through the Cancer Drugs Fund as the standard of care, Blood Cancer UK feel that the decision to compare liso-cel with salvage chemotherapy, high-dose chemotherapy (HDT) and a stem cell transplantation (which is now used infrequently by clinicians) has prevented the committee from realising some of the additional uncaptured benefits of liso-cel for LBCL patients. |
| 3 | There is an undeniably heavy burden faced by LBCL patients in both managing symptoms of disease combined with the toxicity of existing treatments. This negative guidance means those in receipt of axi-cel at the 2L are at a greater risk of experiencing damaging side effects like cytokine release syndrome. Data from the TRANSFORM study highlighted liso-cel's preferable toxicity profile – with just 4% of recipients admitted to ICU compared to 25% in axi-cel's ZUMA-7 trial. Reducing their exposure to damaging side effects is hugely important to LBCL patients, and we are concerned the significance of this is not being considered enough. |
| 4 | We'd also like to emphasise that, in comparison to axi-cel, liso-cel's more favourable safety profile means there's an increased potential that this treatment could be delivered in an outpatient setting – reducing the need for multiple or prolonged hospital visits. This more convenient method of receiving treatment would not only reduce disruption and travel time but also allows patients to be at home for longer with their loved ones. Similarly, as a one-time treatment, it also means those few patients in receipt of the current standard of care commissioned for routine use (salvage chemotherapy, HDT and a stem cell transplantation) can avoid numerous cycles of intensive chemotherapy regimens. Overall, the approval of liso-cel would have a positive impact on the quality of life of LBCL patients and their families and therefore should be given further consideration. |
| 5 | We recognise and appreciate the committee's concerns around cost-effectiveness. However, we are equally concerned that this innovative and clinically effective and superior treatment will not reach patients that will significantly benefit from access to it. Liso-cel would not only allow patients to benefit from the efficacy associated with CAR-T therapies earlier in the pathway (reducing the need to expose them to harsh alternatives) but also open the door to older patients not considered fit enough to receive a transplant. We hope the issues can be addressed and an agreement can |

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

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| | be reached with the company in a way that doesn't impede access to this potentially life-saving treatment for LBCL patients in the future. |
| 6 | |

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | We are concerned that the recommendation has not taken into account the psychological burden and mental strain that comes with the fear of relapse, and that there will be no suitable treatments available. Nearly a half of people with DLBCL and other high-grade B cell lymphomas will sadly |

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| | relapse or not respond to treatment. The prognosis for these patients is poor with limited treatment options. Our patients describe the constant fear of relapse and the symptoms this can cause which include insomnia and anxiety. Having another treatment option available to these patients will provide them with some hope in a very difficult time. |
| 2 | We do not feel that the recommendation has taken the huge impact that the side effects of current treatment have on patients. Often the side effects of treatment are worse than the disease itself and difficult to tolerate. The current clinical practice of high dose chemotherapy has significant side effects which impact the patient and those around them. Symptoms such as fatigue, sickness, diarrhoea and recurrent infections can impact on a person's ability to work or even to carry out normal activities of daily living. This can lead to financial difficulties and an increased burden on family and carers. Liso-cel can provide an option which is better tolerated with potentially fewer side effects. In the 2024 Lymphoma Coalition survey 72% of patients and 80% of carers rated fewer side effects/more tolerable side effects during treatment as being important or very important. This supports our feeling that the side effect profile of liso-cel should have been taken more into account. |
| 3 | We are concerned that the reduced time in hospital when receiving liso-cel compared to current standard treatment has not fully been taken into account. Patients appreciate a treatment which requires less time in hospital, and therefore less disruption to them and their carers. The 2024 lymphoma coalition survey showed that 19% of patients experienced problems travelling to and from treatment centres. |
| 4 | |
| 5 | |
| 6 | |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | nil |
| **Name of commentator person completing form:** | Dr Wendy Osborne |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | The 2nd line comparator of high dose chemotherapy and autologus stem cell transplant is significantly more toxic and less effective than lisocel as shown in the randomised TRANSFORM study. Patients are in hospital for 1 month and have toxicity but yet the high dose chemo and auto |

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| | |
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| | is ineffective in 90% of patients who undergo this treatment (CORAL, ORCHAARD) and is even less effective in the patients who relapse early, this is the group who could access Lisocel |
| 2 | The toxicity profile of Lisocel is minimal and it can be delivered as an outpatient which would have a positive impact on the current bed pressures within the NHS. Many new approved treatments (eg bispecs for myeloma) require inpatient stays of at least 5 days and this has really impacted on bed capacity in many Trusts. To have access to an effective CAR T treatment which can be delivered as an outpatient will save costs but also reduce bed pressures. |
| 3 | In current practice this patient group receive Axi cel and although this is not formally a comparator in the technology appraisal due to 2nd line Axicel currently in the CDF it is what is happening in practice. Axi cel is effective but does have to be given as an impatient with most pts remaining in hospital for at least 7 days post infusion and usually 10-14 days. UK data (Kuhnl et al ASH abstract 2342 Dec 2024) shows that 20% of patients required ITU after 2nd line Axicel and the costs of this ITU admission and the inpatient rehab post ITU which is often 2 weeks does need to considered. We will not see the same level of ITU costs with 2nd line Lisocel. |
| 4 | In draft appraisal in it stated that the EAG are concerned that the drop out between leukapheresis and infusion in TRANSFORM is lower than in clinical practice. The drop out rate we are seeing wuth 2nd line CAR T is much lower than we see in 3rd line (KUHNL et al ASH abstract 2342 Dec 2024), currently 9% inUK real world data. The design of the TRANSFORM study is such that is favours the standard arm compared to ZUMA 7 which did not have early apheresis and cross over built in. The bridging rate in TRANSFORM is lower than in clinical practice but higher than in ZUMA 7 when it was not allowed. Therefore TRANSFORM is more generalisable to UK clinical practice than ZUMA 7, 2nd line Axi-cel in terms of drop out and bridging. |
| 5 | The availablity of polaRCHP first line and subsequent fewer relapses should mean less Liso-cel required for economic UK modelling. |
| 6 | Subsequent treatment costs are changing as the pathway changes. If a patient is failed by 2nd lne CAR T then >80% of these pts would now receive bispeciifc antibody in the UK. If they are failed by 2nd line auto transplant then they would eithere receive 3rd line CAR T or 3rd line bispecifc depending on disease kinetics and pateint fitness. The statement in this draft guidance that “a third of pts would have palliative treatment 3rd line” would now be much lower ue to the availabity of third line bispecifics which can be delivered to much older and less fit patients. |

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# Single Technology Appraisal

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

## Comments on the draft guidance received through the NICE website

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | |
| **Other role** | |
| **Organisation** | Gilead Sciences |
| **Location** | |
| **Conflict** | None |
| **Notes** | |

**Comments on the DG:**

- **Section 3.15 Adverse event costs at third line**

Gilead are concerned that NICE is proposing to include a revised NHS Tariff of £58,964 as the cost of treatment for CAR-T. For the reasons set out below, we consider this decision to be procedurally unfair and unreasonable, and with potential adverse ramifications for patient access to all CAR T treatments.

During the NICE re-appraisal of axicabtagene ciloleucel (axi-cel) in 2022 - Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA872) [1] - Gilead held various discussions with NICE and NHS England on what was the most appropriate CAR T-cell therapy delivery cost to be used by NICE in its assessment of cost effectiveness. At the time, NHS England initially suggested a delivery cost of £96,000. This figure was subsequently reduced to £41,101 following extensive discussions with NICE and NHS England. This adjustment, informed by transparent communication and shared cost inputs, ensured a 'cost of treatment' figure that was both fair and accurate at the time, and aligned with real-world considerations. This figure was then used in the final guidance (TA872, issued by NICE in February 2023). Since then, the CAR T-cell therapy tariff of £41,101 has been consistently applied to all adult CAR T appraisals, including TA893 [2], TA895 [3], and TA975 [4].

We were interested to hear, therefore, the NHS England cancer lead, Professor Peter Clark, inform the Committee for lisocabtagene maraleucel, at its meeting on 2nd October 2024, that the effective CAR T-cell therapy tariff had changed. He stated that this had risen from £41,101, first to £57,080 and now to £58,964. We are therefore concerned about both how this cost was decided, and that the Committee concluded that this should be included as the cost of treatment for this appraisal (as confirmed in section 3.16 of the Draft Guidance).

If it is indeed the case that NHS England now regards the cost of CAR T-cell therapy delivery to be £58,964, then this figure has been reached without external consultation or transparency.

As previously noted in our correspondence with NICE, the recommendations that NICE make must apply a clear and methodological approach, be evidence based and be transparent. To utilise an increased cost of CAR T-cell treatment in an appraisal without such transparency or decision-making, goes against these principles.

Gilead appreciates that there may be broader reasons as to why both NHS England and trusts might favour an increase in tariff amount. However, the evidence underlying any changes should be shared and discussed with all relevant stakeholders. This must include a breakdown of actual costs provided by a representative group of trusts which NHS England has consulted in order to arrive at the updated, proposed, tariff.

We should also like to draw attention to a statement made by the NICE committee in its CDF review of TA559, now updated and replaced by TA872. In the Final Appraisal Document, whilst summarising NHS England's views, the Committee noted that, "while the current tariff represents the high hospital costs of establishing the infrastructure of a CAR T-cell therapy service and delivering a relatively new type of treatment, economies of scale may be expected over time. Particularly with clinical developments in care that reduce toxicity and the need for more intense monitoring and treatment."

Given this context, it is very surprising that NHS England has proposed an increased delivery cost of £58,964, which amounts to a 43% increase. This increase seems inconsistent with the fact that the infrastructure for CAR T-cell therapy delivery within the NHS is now well-established. Additionally, healthcare professionals now have significant experience delivering this treatment, and the expected increase in patient numbers will only further enhance efficiency in NHS delivery. Moreover, we also note that the clinical treatment most similar to CAR-T treatment in terms of complexity and NHS activity is autologous stem cell transplant (ASCT) which has a tariff rate of £17,181 (inflated from 2019/2020 HRG tariff elective SA26A £16,668).3 The discrepancy between the tariff rates for CAR T-cell therapy delivery and ASCT suggests that the proposed cost increase may not accurately reflect the actual resources required for CAR T-cell therapy delivery, especially given the well-established infrastructure and experience which now exists within the NHS.

A 2023 study of 726 UK patients treated with CAR T for relapsing and remitting large B-cell lymphoma also demonstrated that the costs of delivering CAR T should be decreasing with scale and experience. This study showed a significant reduction in incidence of cytokine release syndrome and need for ICU admissions over time, likely reflecting both earlier use of tocilizumab and corticosteroids, and lower disease burden at time of treatment due to improvements in bridging therapy. This and the reduced incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), even with inclusion of older patients, further indicates improvement in toxicity management for CAR T-cell therapy patients.[5] This study demonstrates Gilead's belief that, with increased experience of administering CAR T-cell therapy, NHSE is now able to manage it with less

complications and thus less associated costs. Gilead therefore believes that the CAR T-cell cost of delivery should, if changing at all, be decreasing from the initial tariff cost of £41,101, given that when this tariff cost was agreed when treatment was more time and resource intensive for the NHS.
Use of an increased CAR T-cell therapy delivery cost would have important repercussions for all manufacturers with technologies in this area that are due to undergo assessment by NICE. If the figure is not correct, this will unfairly bias against our own and other CAR T-cell therapies, as they are assessed. Consequently, this will limit patient access to new and life extending treatments which address a significant medical unmet need. This may have stark ramifications for patients and it is therefore vital that there is sufficient transparency on the methods used to calculate the cost of treatment, and agreement amongst stakeholders as to what the correct figure is.
Given the factors explored above, Gilead believe that the CAR T-cell therapy tariff cost of £41,101 should not be increased for current or future NICE appraisals. If NICE does not believe this is the case, Gilead would like to request a detailed breakdown of the costs included within the tariff, the trusts from which these figures were gathered, and the mean and median of the totals by trust. This information is essential for Gilead to assess its position and ensure that future CAR T-cell therapy appraisals are not adversely affected.

References
[1]https://www.nice.org.uk/guidance/ta872
[2]https://www.nice.org.uk/guidance/TA893
[3]https://www.nice.org.uk/guidance/TA895
[4]https://www.nice.org.uk/guidance/TA975
[5]https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.19157?saml_referrer

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | |
| **Other role** | |
| **Organisation** | None |
| **Location** | |
| **Conflict** | None |
| **Notes** | |
| **Comments on the DG:** | |

- **Has all of the relevant evidence been taken into account?**

I will compare Lisa-cel with Axi-cel as this is the real comparator (I know the NICE rules around this but they are frankly rather silly).

I work in a CAR T infusion centre. The use of Lisa-cel is foundational for us to be able to improve services for our patients as it will enable development of an ambulatory care model for CAR delivery. This will profoundly help capacity on our haematology ward which is under severe strain currently. The reduced ITU use will also enable other NHS commitments to be

delivered such as curative cancer surgery (when ITU is full, major operations are postponed).

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

As above - the use of lisa-cel will enable quite significant cost savings compared with axi-cel around inpatient stay and ITU use. The significant reduction of ICANs means that rehabilitation (which can be prolonged following grade 4 ICANs) will be less needed. This will be a huge benefit for our ITU / ward and allied health care professional capacity issues.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

No - approval of lisa-cel is key for us to be able to sustainable deliver all the commissioned services for cancer the NHS demand of us.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

I don't think so.

# EAG Response and Critique to Company Draft Guidance Comments for lisocabtagene-maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable [ID3887]


| | |
|---|---|
| **Produced by** | *Warwick Evidence* |
| **Authors** | *Angela Mwape, Research Associate, University of Warwick*<br>*Daniel Gallacher, Assistant Professor, University of Warwick* |
| **Correspondence to** | *Daniel Gallacher, Warwick Medical School, d.gallacher@warwick.ac.uk* |
| **Date completed** | *16/12/2024* |

The company comments on the draft guidance are structured into three issues, which the EAG responds to in turn. The company also provides a summary outlining arguments why liso-cel could be considered more favourable than axi-cel. The EAG does not consider axi-cel a relevant comparator as it is currently only available through managed access.

**Pricing details**

The company presents additional analyses and a revised base-case ICER, changing some key assumptions and also a revised PAS discount from the previous submission.

The list price of liso-cel is £297,000. The previous PAS discount price was £[redacted] reflecting a discount of [redacted]%, however this has changed to £[redacted] ([redacted]% discount).

The previously used CAR T tariff cost of £41,101 has been updated to £58,964. The analyses conducted by the company and EAG in this document use the list-price for comparator therapies. Analyses where the commercial discounts have been applied are presented in the EAG cPAS appendix.

**Issue 1: Inclusion of ICU costs**

The company stated that they previously believed intensive care unit (ICU) resource use costs were included in the CAR T and HSCT tariff costs, and so did not require separate modelling. Having received confirmation from NHS England that these costs are not included, the company now models them separately for all second line (2L) and 3L treatments. The EAG considers this inclusion appropriate.

**<u>Proportion requiring ICU stay</u>**

For the proportion of people requiring an ICU stay, the company use data from an unpublished RWE study of CAR T use in France, despite data being available from TRANSFORM and ZUMA-7.

**Table 1: Overview of estimates for proportions requiring ICU admission.**

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

The EAG notes that the company reports there are no plans for this data to become published. This RWE study was sponsored by the company, and the report received by the EAG showed evidence of being altered by the company's HTA team. (NICE notes that the company has clarified that the amendments relate to checking the accuracy of the translation from the original French to English.) The EAG is unable to independently verify the accuracy of the data. The study's aims were:

- PRIMARY: To describe the journey of CAR T-cell-treated patients in France and the main treatment phases
- SECONDARY: To describe the patients' characteristics.
- SECONDARY: To identify the predictors of the patient's journey.

The EAG considers these aims vague and not wholly addressed within the report provided.

Assuming the reliability of the report, the estimates coming from the study are subject to limitations including the small number of people contributing information for liso-cel (n=[redacted]), and the lack of randomised comparison between the two therapies. Both estimates from the study are for 2L populations, however for axi-cel in the model they are applied at 3L. This is despite the RWE clearly including 3L axi-cel (n=[redacted]) initially, but these patients have been disregarded as the rest of the report focuses on 2L.

The EAG is unclear why, given the apparent benefits of liso-cel, the vast majority of this population received axi-cel ([redacted]). If this is due to the differing timings of implementation of the technologies, the EAG is concerned that axi-cel outcomes may have improved as CAR T use has become more widespread and clinicians gain experience, and that using historical data may not represent current axi-cel usage and hence be a source of bias. This is confirmed by the EAG's clinical expert who stated there is now more aggressive ward management of axi-cel patients to avoid

ICU admission. Hence the differences between the therapies observed in the data are unlikely to be solely attributable to the choice of therapy.

The company maintains using an estimate for the proportion of people receiving 2L SOC to require an ICU stay based on TRANSFORM ([redacted]%). The EAG is unable to verify this estimate, but assumes this does not include ICU admissions related to subsequent therapies. As SOC is the comparator, the EAG considers it most consistent to maintain the use of the equivalent 2L value for liso-cel ([redacted]%).

For 3L auto-SCT and allo-SCT, the company uses estimates of ICU requirement derived from TRANSFORM, whilst for chemotherapy uses clinical expert opinion. The company noticeably do not report the value specific to 3L CAR T. Given values for other 3L treatments have been reported from TRANSFORM, the EAG are concerned by this omission.

For 3L ICU admissions relating to subsequent CAR T, the EAG prefers to use the value for the French RWE given the lack of value available from TRANSFORM, which is also preferred by the company. The EAG accepts that an estimate from TRANSFORM would likely underestimate ICU admissions for axi-cel, as 3L liso-cel was received, rather than axi-cel, but this estimate would provide a helpful benchmark in determining which value for axi-cel is most appropriate.

**Duration of ICU stay**

For the length of ICU stay, the company assume equivalent duration of stay for liso-cel, axi-cel and other treatments. The estimate of 7.5 days comes from clinical expert opinion from TA872.

The EAG is unclear why the company has reported median rather than mean values for comparative purposes, however is content with the assumption of equivalent durations for each treatment, and considers all estimates to be similar. The EAG's clinical expert noted that this assumption comparing axi-cel and liso-cel could be conservative, as toxicities related to axi-cel are more common and harder to treat. For other treatments, a comparison is much harder as ICU durations would be much more variable.

**Table 2: Overview of estimates for duration of ICU stay**

| | Estimate Duration of ICU Stay |
|---|---|
| French RWE Study: axi-cel | [redacted] |
| French RWE Study: liso-cel | [redacted] |
| ZUMA 7: axi-cel | Median = 8 days |
| TRANSFORM: liso-cel | Median = [redacted] days |
| Experts from TA872 | 7-8 days |

**Issue 2: Inclusion of 3L AEs**

Previously the company aimed to exclude the costs of AEs occurring in 3L, however these were modelled for 3L CAR T as they were included in the tariff calculation. The committee preference was to exclude the AE contribution from the tariff cost at 3L to provide a fairer analysis.

In this current submission, the company include 3L AE costs for both arms. This is achieved by modelling a set-cost for AEs

For 3L CAR T, these costs are assumed to be captured in the tariff cost. For all other subsequent treatments, a standard cost of £7,310 is applied, indicating that in terms of average cost of treating AEs per patient receiving each treatment, there is no difference between auto-SCT, allo-SCT, chemotherapy and radiotherapy for treating AEs. This cost used by the company is derived from the costs of 2L SOC which was based on TRANSFORM data.

The EAG's clinical expert stated that the costs associated with allo-SCT are likely to be much higher than the other treatments. As the proportion receiving allo-SCT is much larger for the liso-cel arm in the company base case than for SOC, this assumption likely introduces bias in favour of liso-cel. The EAG is unclear why the company could not produce treatment specific estimates from their 2L, or even 3L data from TRANSFORM. The EAG is unable to explore alternative approaches given the limited time available for this critique.

### Issue 3: Uncaptured benefits

The company submits three subpoints outlining benefits of liso-cel over axi-cel. These focus around additional cost-saving and better patient quality of life due to liso-cel being associated with an improved safety profile adverse events and higher administration in an outpatient setting. These could increase ICU and bed capacity in hospitals.

The EAG sympathises with the points raised by the company, however their relevance is limited due to the fact that axi-cel is not deemed a relevant comparator due to only being available in managed access. The EAG's clinical expert agreed that liso-cel infusion could be administered in an outpatient setting once clinicians became familiar with the treatment, whilst this is unlikely for axi-cel.

The EAG notes that the company's points relate to a comparison at 2L, however their scenario analyses exploring this impact use liso-cel at 2L and axi-cel at 3L. The EAG are unsure on the breakdown of the current CAR T tariff cost, but present some scenarios exploring the potential benefit claimed by the company.

### Company analyses

The EAG was unable to implement the old company base case on the new company model, and requested instructions for doing so from the company. The EAG observed that the instructions produced in ICER of [redacted] which disagreed slightly with the ICER from the previous model of [redacted]. This discrepancy is small and can probably be ignored.

### Additional changes

In addition to the changes mentioned above, the company makes some further revisions to their base-case modelling.

Firstly they accept the committee's preference to use cycle based discounting, and to assume 80% of people in both liso-cel and SOC arms who experience a time-to-next treatment event receive a subsequent treatment.

The company also uses updated sources for the costs of 2L AE management in the model, which only affects the SOC arm. The affected AEs are shown in Table 3. These increases the AE costs for SOC from £[redacted] to £[redacted].

The EAG is unable to discern whether these changes mark an improvement in the modelling. The company appears to have pooled multiple AEs in their most recent calculations. As no issue was raised with these costs previously, and that minimal justification is provided to support the company's claim that they are "more appropriate", the EAG prefers to use the old AE costs.

**Table 3: Main updates to AE management costs**

| AE | Old Cost | New Cost |
|---|---|---|
| Neutropenia<br>Prolonged cytopenia | £2,336 (NHS ref costs)<br>£2,708 (NHS ref costs) | £1,773 (alternate NHS ref costs) |
| Anaemia | £1,603 (NHS ref costs) | £2,801 (alternate NHS ref costs) |
| Febrile Neutropenia | £2,336 (NHS ref costs) | £5,622 (alternate NHS ref costs) |

Additionally, the company also adds costs for rehab after ICU-related neurotoxicity, based on an assumption of 14 days at a cost of £710.68 per day. The duration is estimated by the company's clinical advisors, and the daily cost is based on NHS reference costs. This is applied for all grade ≥3 case of neurotoxicity, bringing the cost of AEs for SOC to £[redacted].

The final change is to include ward management costs for grade 1/2 neurotoxicity and CRS, which are estimated on the management cost of febrile neutropenia, and cumulatively brings the AE management cost for SOC to £[redacted].

The impact of each change is shown in Table 4.

**Table 4: Impact of changes from previous to current company base case.**

| | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|
| Previous Company Base Case | [redacted] | [redacted] | [redacted] |
| 1) Updated CAR T tariff cost of £58,964 | [redacted] | [redacted] | [redacted] |
| 2) Apply 80% subsequent therapy | [redacted] | [redacted] | [redacted] |
| 3) Revised PAS | [redacted] | [redacted] | [redacted] |
| 4) Inclusion of ICU costs[a] | [redacted] | [redacted] | [redacted] |
| 5) Inclusion of 3L AEs[a] | [redacted] | [redacted] | [redacted] |
| 6) Cycle-based discounting[a] | [redacted] | [redacted] | [redacted] |
| 7) Source of AE costs[a] | [redacted] | [redacted] | [redacted] |
| 8) Added hospital ward stay costs[a] | [redacted] | [redacted] | [redacted] |
| 9) Added rehab costs post ICU[a] | [redacted] | [redacted] | [redacted] |
| New Company Base Case (1-9)[a] | [redacted] | [redacted] | [redacted] |

a – was obtained from new company model

### Committee Preferred Assumptions

The committee preferred assumptions aligned with the original company base case on most issues, but specified:

- Use of updated CAR T tariff cost
- Apply 80% subsequent therapy assumption for both arms
- Use cycle-based discounting

Here the EAG presents models and scenarios based on the committee's preferred assumptions (changes 1-3, 6), with and without the new model functionality (company changes 4,8,9). The impact of changes 5 and 7 are explored through scenarios. When applying ICU, the EAG uses the TRANSFORM study but uses the alternative source in a scenario.

Previously, the committee preferred to subtract AE costs for 3L axi-cel. The company reported that the calculation of these AE costs included ICU related costs, and so removed them from this calculation as a correction. The EAG accepts this correction, and it is used where applicable in these analyses.

The EAG also presents additional scenarios building from the committee preferred analyses.

**Table 5: Committee preferred assumptions**

| | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|
| Committee preferred assumptions (old model function) | [redacted] | [redacted] | [redacted] |
| a) Include 3L AE costs | [redacted] | [redacted] | [redacted] |
| b) Updated source of AE costs | [redacted] | [redacted] | [redacted] |
| c) 50% outpatient delivery of liso-cel | [redacted] | [redacted] | [redacted] |
| d) AE costs of liso-cel reduced | [redacted] | [redacted] | [redacted] |
| e) c+d | [redacted] | [redacted] | [redacted] |
| Committee preferred assumptions (new model function) | [redacted] | [redacted] | [redacted] |
| a) Include 3L AE costs | [redacted] | [redacted] | [redacted] |
| b) Updated source of AE costs | [redacted] | [redacted] | [redacted] |
| c) Use RWE for liso-cel ICU proportion | [redacted] | [redacted] | [redacted] |
| d) 50% outpatient delivery of liso-cel | [redacted] | [redacted] | [redacted] |
| e) AE costs of liso-cel reduced | [redacted] | [redacted] | [redacted] |
| f) d+e | [redacted] | [redacted] | [redacted] |

**Additional EAG Comments**

The EAG notes that the committee's preference was largely to use inputs sourced from the TRANSFORM trial, despite acknowledging the limited generalisability of the trial to NHS care. The EAG considers that the committee's preference to change one key parameter (the proportion receiving subsequent therapies) to deviate from the TRANSFORM study to be unusual, and inconsistent with its general preference to align the costs and benefits.

The EAG is still concerned about the assumptions of the modelling from this appraisal which result in a large benefit of liso-cel relative to modelling of axi-cel in TA895, which is inconsistent with available evidence for these treatments at 3L.

The EAG previously explored using external sources to inform the survival modelling, which the committee was reluctant to use. The EAG maintains that incorporating external information from a larger trial with longer follow-up remains optimal for decision-making but will only present analyses using this approach on request from committee.

The EAG maintains some other changes from its previous base case, as shown in Table 6, to improve the relevance of the modelling to the NHS population. These were to use UK-based estimates for the proportion of people receiving bridging therapy, to set the starting age to 59, and to use the distribution of subsequent therapies as estimated by UK clinical experts.

**Table 6: Changes from current company to EAG base case**

| | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|
| Company Base Case | [redacted] | [redacted] | [redacted] |
| 1) Use ICU proportion for liso-cel from TRANSFORM | [redacted] | [redacted] | [redacted] |
| 2) Use distribution of subsequent therapies based on expert opinion | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| 3) Use previous AE management costs | [redacted] | [redacted] | [redacted] |
| 4) Bridging therapy from Boyle et al. (89%) | [redacted] | [redacted] | [redacted] |
| 5) Model starting age of 59 | [redacted] | [redacted] | [redacted] |
| EAG Base Case | [redacted] | [redacted] | [redacted] |

The EAG remains concerns about the optimistic extrapolations for both arms coming the trial data, owing to both its generalisability and immaturity. Hence the EAG explores applying the exponential distribution for OS for both arms, which produced the lowest cure fraction estimate for both arms (Table 7). The AIC and BIC for all fitted models were similar.

The EAG also examines the impact of removing 3L AE costs due to the potential for bias from the way the company has applied non-CAR T associated costs. Additionally, the EAG presents scenarios exploring the potential benefits of liso-cel over axi-cel in the form of lower AE management costs relative to the CAR T tariff cost, and administration in an outpatient setting. Both of these are based on assumptions and the EAG is unable to verify their suitability for decision-making.

**Table 7: EAG Scenario Analyses**

| | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|
| EAG Base Case | [redacted] | [redacted] | [redacted] |
| 1) Use exponential OS parametric models | [redacted] | [redacted] | [redacted] |
| 2) Remove 3L AE Costs | [redacted] | [redacted] | [redacted] |
| 3) Use updated AE management costs | [redacted] | [redacted] | [redacted] |
| 4) 50% outpatient delivery of liso-cel | [redacted] | [redacted] | [redacted] |
| 5) AE costs of liso-cel reduced | [redacted] | [redacted] | [redacted] |
| 6) 4+5 | [redacted] | [redacted] | [redacted] |