

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Appraisal**

**Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma**

**Draft scope**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of tisagenlecleucel-T within its marketing authorisation for treating relapsed or refractory diffuse large B-cell lymphoma.

**Background**

Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Lymphomas are divided into Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphomas (NHL) are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. The most common B-cell lymphomas are follicular lymphoma (FL) which is a slow growing, low grade form of NHL and diffuse large B-cell lymphomas (DLBCL), a fast growing, high grade form of NHL. Some FLs transform into high grade DLBCL (transformed high grade FL). The symptoms differ depending on which organ or tissues are affected by the lymphoma. NHL often presents as painless lumps (enlarged lymph nodes) in the neck, armpit or groin but sometimes may start in other parts of the body such as the stomach or bowel (extranodal disease). People may also have loss of appetite, tiredness or night sweats.

There were around 11,690 new cases of non-Hodgkin lymphoma (NHL) in England in 2015 with 4,688 of these being for DLBCL.<sup>1</sup> Most people diagnosed with DLBCL are 65 or over. Survival rates at 5 years for DLBCL are around 65-70% for stage I and II and around 50% at stages III and IV.<sup>2</sup>

The most widely used first-line treatment for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). Sometimes etoposide is added to this regimen. NICE guideline NG52 recommends chemotherapy in combination with rituximab for relapsed or refractory disease followed by stem cell transplantation. Chemotherapy regimens commonly used in clinical practice include DHAP (dexamethasone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide) and IVE (ifosfamide, etoposide, epirubicin). If stem cell transplantation is not suitable, further chemotherapy or immunotherapy may be used alone. NICE technology appraisal 306 recommends pixantrone monotherapy for people who have multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma, when they have been treated previously with rituximab and are the third or fourth line of treatment.

### The technology

Tisagenlecleucel-T also known as CTL019 (Kymriah, Novartis) is a chimeric antigen receptor (CAR) T cell therapy that modifies the patient's blood cells to target a protein called CD19. It is administered as an intravenous infusion once only.

Tisagenlecleucel-T does not currently have a marketing authorisation in the UK for treating DLBCL. It is being studied in a phase II single arm clinical trial in people with relapsed or refractory DLBCL after 2 or more lines of therapy and who are ineligible for autologous stem cell transplantation (defined as autologous stem cell transplant failing, or not being eligible or not consenting to autologous stem cell transplant).

<b>Intervention(s)</b>	Tisagenlecleucel-T
<b>Population(s)</b>	People with relapsed or refractory diffuse large B-cell lymphoma
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Established clinical management without tisagenlecleucel-T including but not limited to: <ul style="list-style-type: none"> <li>○ pixantrone monotherapy</li> <li>○ salvage chemotherapy with or without rituximab [DHAP (dexamethasone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide), IVE (ifosfamide, etoposide, epirubicin)]</li> </ul> </li> <li>• Axicabtagene ciloleucel (subject to ongoing NICE appraisal)</li> <li>• Best supportive care (including radiotherapy)</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression free survival</li> <li>• response rate</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.</p> <p>The availability and cost of biosimilars should be taken into account.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">‘Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma’</a> (2014). NICE Technology Appraisal 306. Review date to be confirmed.</p> <p><b>Terminated appraisals</b></p> <p><a href="#">‘Rituximab for aggressive non-Hodgkin's lymphoma’</a> (withdrawn appraisal – routinely used outside its licensed indication in clinical practice) (2003). NICE Technology Appraisal 65.</p> <p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">‘Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma’</a> NICE technology appraisals guidance [ID1115]. Publication date to be confirmed.</p> <p><a href="#">‘Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma’</a> NICE technology appraisals guidance [ID986]. Suspended – company advised that they would not be seeking regulatory approval from the European Medicines Authority for this indication.</p> <p><a href="#">‘Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma’</a> NICE technology</p>

	<p>appraisals guidance [ID407]. Suspended due to ongoing regulatory discussions regarding the licence for this drug.</p> <p><b>Related Guidelines:</b></p> <p><a href="#">‘Non-Hodgkin’s lymphoma: diagnosis and management’</a> (2016) NICE Guideline 52. Review date to be confirmed.</p> <p><a href="#">‘Haematological cancers: improving outcomes’</a> (2016). NICE Guideline 47. Review date to be confirmed.</p> <p><a href="#">Non-Hodgkin's lymphoma: rituximab subcutaneous injection</a> (2014) NICE evidence summary of new medicines 46.</p> <p><b>Related Quality Standards:</b></p> <p><a href="#">Haematological cancers</a> (2017) NICE quality standard 150.</p> <p><b>Related NICE Pathways:</b></p> <p><a href="#">Blood and bone marrow cancers</a> (2016) NICE pathway</p>
<p><b>Related National Policy</b></p>	<p>Department of Health (2016) <a href="#">NHS outcomes framework 2016 to 2017</a>: Domains 1–5.</p> <p>NHS England (2017) <a href="#">Next steps on the five year forward view</a></p> <p>NHS England (2017) <a href="#">Manual for Prescribed Specialised Services 2017/18</a>. Chapter 105.</p> <p>NHS England (2013) <a href="#">NHS standard contract for cancer: Chemotherapy (Adult) Section B part 1 Service specifications</a>. Clinical Commissioning Policy. Reference B15/S/a.</p>

### Questions for consultation

Have all relevant comparators for tisagenlecleucel-T been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory diffuse large B-cell lymphoma after 2 or more lines of therapy and who were ineligible for autologous stem cell transplantation?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom tisagenlecleucel-T is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma will fit into the existing NICE pathway, [Blood and bone marrow cancers](#)?

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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tisagenlecleucel-T will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider tisagenlecleucel-T to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of tisagenlecleucel-T can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

NICE has published an addendum to its guide to the methods of technology appraisal (available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum->

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[cost-comparison.pdf](#)), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

### References

1. Office of National Statistics (2017) [Cancer Registration Statistics: England 2015](#) [accessed November 2017].
2. Cancer Research UK (2015) [Survival for high grade lymphomas](#) [accessed November 2017].