NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin's lymphoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of axicabtagene ciloleucel within its marketing authorisation for treating relapsed or refractory low-grade non-Hodgkin's lymphoma.

Background

Lymphomas are cancers of the lymphatic system, which is part of the body's immune system. They are divided into Hodgkin's and non-Hodgkin's lymphomas. Non-Hodgkin's lymphomas are a heterogeneous group of conditions ranging from 'indolent' (low-grade) to 'aggressive' (high-grade) depending on the rate at which the abnormal lymphocytes divide. Indolent lymphomas are slow growing, with long median survival times but are less likely to be cured by treatment.

Follicular lymphoma is the most common type of indolent non-Hodgkin's lymphoma. Patients with follicular lymphoma typically present with painless, swollen lymph nodes in the neck, armpit or groin. Lymphomas are commonly staged I (best prognosis) to IV (worse prognosis). The stage of the lymphoma reflects how many groups of lymph nodes are affected, where they are in the body, and whether other organs such as the bone marrow or liver are affected. Most people (80%) present with advanced disease (stage III to IV).

Marginal zone lymphoma is another type of indolent non-Hodgkin's lymphoma that develops from B lymphocytes that are normally found at the edge of areas of lymph node tissue. Mucosa associated lymphoid tissue (MALT) lymphoma is the most common type of marginal zone lymphoma and it most commonly affects the stomach. Nodal marginal zone lymphoma starts in the lymph nodes and splenic marginal zone lymphoma starts in the spleen but can also be found in the bloodstream.[1]

In 2017, approximately 12,000 people were diagnosed with non-Hodgkin's lymphoma in England, of whom around 18% had follicular lymphoma.[1,2] The 5-year survival rate is between 80 to 90% for people with follicular lymphoma and is between 50 to 80% for marginal zone lymphoma depending on the stage of disease.[3]

For untreated disease:

- NICE technology appraisal guidance 243 recommends rituximab in combination with chemotherapy as an option for untreated symptomatic stage III and IV follicular lymphoma.

- NICE technology appraisal guidance 513 recommends obinutuzumab in combination with chemotherapy as induction treatment followed by

obinutuzumab as maintenance therapy for people who have a Follicular Lymphoma International Prognostic Index of 2 or more.

- For people who do not have symptoms, the NICE clinical guideline for non-Hodgkin's lymphoma recommends that rituximab is given alone, although at the time of writing this scope rituximab monotherapy did not have a marketing authorisation in the UK for untreated non-Hodgkin's lymphoma.

For treated disease:

- People whose disease does not respond to treatment, or relapses after treatment is completed, will usually receive a different combination chemotherapy regimen, with or without rituximab. Stem cell transplantation may also be considered.

- NICE technology appraisal guidance 137 recommends rituximab in combination with chemotherapy or as monotherapy for relapsed stage III or IV follicular non-Hodgkin's lymphoma.

- NICE technology appraisal guidance 226 recommends rituximab maintenance therapy as an option for people whose follicular non-Hodgkin's lymphoma has responded to first-line induction therapy with rituximab in combination with chemotherapy.

- NICE technology appraisal guidance 627 recommends lenalidomide in combination with rituximab as an option for previously treated follicular lymphoma in adults.

- NICE technology appraisal guidance 629 recommends obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance as an option for treating follicular lymphoma that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen.

The technology

Axicabtagene ciloleucel (Yescarta, Kite, a Gilead company) is a type of immunotherapy that uses autologous T cells directed against the tumour antigen CD19. It is administered intravenously.

Axicabtagene ciloleucel has a marketing authorisation for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma and primary mediastinal large B-cell lymphoma, after 2 or more lines of systemic therapy. It does not currently have a marketing authorisation in the UK for treating relapsed or refractory low-grade non-Hodgkin lymphoma. It is currently being studied in a clinical trial in adults with relapsed or refractory follicular lymphoma or marginal zone lymphoma after at least 2 prior treatments.

Intervention(s)	Axicabtagene ciloleucel
Population(s)	Adults with relapsed or refractory non-Hodgkin's lymphoma

Comparators	• Rituximab monotherapy • Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Established clinical management without axicabtagene ciloleucel • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator technologies and subsequent treatment technologies will be taken into account.
Other considerations	The availability and cost of biosimilar and generic products should be taken into account. 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.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab' (2020). NICE Technology Appraisal 629. 'Lenalidomide with rituximab for previously treated follicular lymphoma' (2020). NICE technology appraisal guidance 627. 'Idelalisib for treating refractory follicular lymphoma' (2019).

	NICE technology appraisal guidance 604. 'Obinutuzumab for untreated advanced follicular lymphoma' (2018). NICE Technology Appraisal 513. 'Rituximab for the first-line treatment of stage III-IV follicular lymphoma' (2012). NICE Technology Appraisal 243. Review date August 2014. 'Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma' (2011). NICE Technology Appraisal 226. Review date August 2014. 'Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma' (2008). NICE Technology Appraisal 137. Review decision March 2011: static guidance list. Terminated appraisals 'Bendamustine for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab' (terminated appraisal) (2010). NICE technology appraisal 206 'Rituximab for aggressive non-Hodgkin's lymphoma' (withdrawn appraisal – routinely used outside its licensed indication in clinical practice) (2003). NICE Technology Appraisal 65. Appraisals in development (including suspended appraisals) 'Ofatumumab in combination with chemotherapy for follicular lymphoma; second line refractory to rituximab' NICE technology appraisal guidance (suspended) [ID1487]. 'Ibrutinib for treating relapsed or refractory follicular lymphoma' NICE technology appraisal guidance [ID1251]. Publication date to be confirmed. 'Duvelisib for treating relapsed follicular lymphoma after 2 systemic therapies' NICE technology appraisal guidance (suspended) [ID1090]. 'Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma' NICE technology appraisal guidance (suspended) [ID407]. Related Guidelines: 'Non-Hodgkin's lymphoma: diagnosis and management' (2016) NICE Guideline 52. Review date to be confirmed. 'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Review date to be confirmed. 'Non-Hodgkin's lymphoma: rituximab subcutaneous injection' (2014) NICE evidence summary of new medicines 46. 'Suspected cancer: recognition and referral' (2015). NICE guideline 12. Reviewed 2021. Related Quality Standards:

	'Haematological cancers' (2017) NICE quality standard 150. Related NICE Pathways: Non-Hodgkin's lymphoma (Updated 2021) NICE pathway Blood and bone marrow cancers (2016) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105. Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for axicabtagene ciloleucel been included in the scope?

Are the outcomes listed appropriate?

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

Where do you consider axicabtagene ciloleucel will fit into the existing NICE pathway, Non-Hodgkin's lymphoma?

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 axicabtagene ciloleucel 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 axicabtagene ciloleucel 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 axicabtagene ciloleucel 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-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 Cancer Research UK (2014) Different types of non Hodgkin lymphoma. Accessed May 2021.

2 Office for National Statistics (2019) Cancer registration statistics, England: 2017. Accessed May 2021.

3 Cancer Research UK (2004–11) Non Hodgkin lymphoma survival statistics. Accessed May 2021.