Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

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 diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies.

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 ('aggressive'), high-grade form of NHL. Primary mediastinal large B-cell lymphoma (PMBCL) is a rare type of NHL which develops in the mediastinum. The symptoms differ depending on what organ or tissues the lymphoma is affecting. 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 with NHL may also have loss of appetite, tiredness or night sweats.

There were around 12,065 new cases of non-Hodgkin lymphoma (NHL) in England in 2017 with 6,391 (53%) of these being DLBCL[1]. Approximately 2-4% of NHL diagnoses in the UK are PMBCL[2]. Most people diagnosed with DLBCL are 65 or over[3]. Survival rate at 5 years for DLBCL is around 60%[4].

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. For relapsed or refractory disease after 1 systemic therapy, NICE guideline NG52 recommends multi-agent chemotherapy, potentially in combination with rituximab, followed by stem cell transplantation for people who are fit enough to have it. Chemotherapy regimens commonly used in clinical practice include DHAP (dexamethasone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide) or IVE (ifosfamide, etoposide, epirubicin). If stem cell transplantation is not suitable, further chemotherapy or immunotherapy may be used alone. The British Society for Haematology recommends that the choice of chemotherapy regimen for relapsed or refractory PMBCL should be the same as those used for treating DLBCL, with consolidation stem cell transplantation for responsive disease[2].

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NICE technology appraisal 306 recommends pixantrone monotherapy for people whose disease has multiply relapsed, been treated previously with rituximab and are on the third or fourth line of treatment. NICE technology appraisal 567 recommends tisagenlecleucel therapy for use within the Cancer Drugs Fund as an option for treating relapsed or refractory DLBCL in adults after 2 or more systemic therapies[a]. NICE technology appraisal 649 recommends polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory DLBCL in adults who cannot have a haematopoietic stem cell transplant.

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 the treatment of adults with relapsed or refractory DLBCL and PMBCL, after 2 or more lines of systemic therapy.

Intervention(s)	Axicabtagene ciloleucel
Population(s)	Adults with relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after 2 or more systemic therapies

Comparators	Established clinical management without axicabtagene ciloleucel including but not limited to:
	• chemotherapy with or without rituximab and with or without stem cell transplantation, such as:
	  ○ DHAP (cisplatin, cytarabine, dexamethasone)
	  ○ GDP (cisplatin, gemcitabine, dexamethasone)
	  ○ ICE (ifosfamide, carboplatin, etoposide)
	  ○ IVE (ifosfamide, epirubicin and etoposide)
	• pixantrone monotherapy
	• polatuzumab vedotin with rituximab and bendamustine (only in people who are not eligible for haematopoietic stem cell transplantation)
	• tafasitamab with lenalidomide (in people who are not eligible for autologous stem cell transplantation and subject to NICE appraisal)
	• best supportive care (including radiotherapy).

[a] Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. https://www.nice.org.uk/Media/Default/About/what-we-do/NICEguidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-positionstatement.pdf

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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 and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention 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: 'Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma' (2014). NICE Technology Appraisal 306. Review date to be confirmed. 'Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies' (2019). NICE Technology Appraisal 559. 'Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies' (2019). NICE Technology Appraisal 567. Review date to be confirmed. 'Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma'

	(2020). NICE Technology Appraisal 649. Review date to be confirmed. Terminated appraisals 'Rituximab for aggressive non-Hodgkin's lymphoma' (2003). NICE Technology Appraisal 65. 'Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma.' (2016) NICE Technology Appraisal 986. Appraisals in development (including suspended appraisals) 'Lisocabtagene maraleucel for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma' NICE technology appraisals guidance [ID1444]. Suspended. 'Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma.' NICE technology appraisals guidance [ID3795]. Publication expected August 2022. 'Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies' NICE technology appraisals guidance [ID3943]. Publication date to be confirmed. 'Glofitamab for treating relapsed or refractory diffuse large B-cell after 2 or more systemic therapies' NICE technology appraisals guidance [ID3970]. Publication date to be confirmed. 'Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma when a stem cell transplant has failed or is unsuitable' NICE technology appraisals guidance [ID4045]. Publication date to be confirmed. 'Lisocabtagene maraleucel for transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas' Proposed NICE technology appraisal [ID3887]. Publication date to be confirmed. Related Guidelines: Haematological cancers: improving outcomes (2016) NICE guideline 47. Non-Hodgkin's lymphoma: diagnosis and management (2016) NICE guideline 52. Review date to be confirmed. Non-Hodgkin's lymphoma: rituximab subcutaneous injection (2014) NICE evidence summary 46. Related Quality Standards: 'Haematological cancers' (2017). NICE quality standard 150.
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

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	Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1-5. 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?

- What chemotherapy regimens are used in clinical practice for DLBCL and PMBCL after 2 or more systemic therapies?

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?

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 is 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.

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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).

References

1. Office for National Statistics. Cancer Registration Statistics, England, 2017. Office of National Statistics. Accessed January 2022.

2. Cwynarski K et al. (2019) The management of primary mediastinal B-cell lymphoma: a British Society for Haematology Good Practice Paper. British Journal of Haematology 185(3): 402-409

3. Diffuse large B-cell lymphoma. Lymphoma action. Accessed January 2022.

4. Survival for high grade lymphomas. Cancer Research UK. Accessed January 2022.