NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lisocabtagene maraleucel for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma

Final scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lisocabtagene maraleucel within its marketing authorisation for treating relapsed or refractory aggressive B-cell non-Hodgkin 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 usually a slow growing, low grade ('indolent') form of NHL, and diffuse large B-cell lymphoma, (DLBCL), a fast-growing, high-grade ('aggressive') form of NHL. DLBCL can occur as a primary tumour (de novo), or when another low-grade lymphoma type transforms to acquire high-grade DLBCL features (for example, transformed FL or chronic lymphocytic leukaemia following Richter's transformation). High-grade B-cell lymphoma (HGBL) is a category of NHL introduced in 2017 by the WHO[1], which is clinically and biologically distinct from DLBCL. People with HGBL have a worse prognosis than those with DLBCL[2]. There are 2 categories of HGBL: those with rearrangements in the *MYC* and *BCL2* and/or *BCL6* genes, and those without such rearrangements. Primary mediastinal large B-cell lymphoma (PMBCL) is a rare type of high-grade NHL which develops in the mediastinum. FL grade 3B is regarded as high grade and is often treated like DLBCL. Mantle cell lymphoma (MCL) is a rare and often high-grade form of NHL that arises from cells in a region called the mantle zone. The symptoms of NHL 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 may also have loss of appetite, tiredness or night sweats.

There were around 12,065 people diagnosed with NHL in England in 2017, with around 6,391 (53%) of these being for DLBCL and 2,168 (18%) for FL[3]. Most people (80%) with FL present with advanced disease, and 10-70% of low-grade FL transforms into a high-grade form[4]. Approximately 2-4% of NHL diagnoses in the UK are PMBCL[5]. Only a small proportion of patients with

NHL have MCL (around 75 people are diagnosed with MCL in the UK each year, which is less than 1% of people who have NHL)[6]. Most people diagnosed with DLBCL are 65 or over[7]. Survival rates at 5 years for DLBCL are around 65-70% for stage 1 and 2 and around 50% at stages 3 and 4[8].

In clinical practice, DLBCL (de novo or transformed), HGBL, PMBCL, FL grade 3B and MCL are often treated similarly. The most widely used first-line treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). Sometimes etoposide is added to this regimen. NICE guideline NG52 recommends that consolidation radiotherapy should be considered for people with advanced-stage DLBCL that has responded to first-line immunochemotherapy, and central nervous system-directed prophylactic therapy for people with risk factors. NG52 also recommends offering salvage therapy with multi-agent immunochemotherapy to people with relapsed or refractory DLBCL followed by stem cell transplantation. 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 salvage regimen for PMBCL should be the same as those used for treating DLBCL, with consolidation stem cell transplantation for responsive disease[5]. NG52 recommends rituximab in combination with chemotherapy as an option for induction treatment in people with relapsed stage 3 or 4 FL, and rituximab monotherapy as an option for the treatment of people with relapsed or refractory stage 3 or 4 FL when all alternative treatment options have been exhausted. Consolidation stem cell transplantation should be considered in patients fit enough to receive it. There is no accepted standard of care for treating MCL in people who have had at least 2 previous lines of therapy. A range of chemotherapy regimens are used, some including rituximab, even though many people will have had rituximab as part of first-line and maintenance treatment.

NICE technology appraisal 306 (TA306) recommends pixantrone monotherapy for people with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma, when they have received previous treatment with rituximab and are in the third or fourth line of treatment. NICE technology appraisal 559 (TA559) recommends axicabtagene ciloleucel therapy for use within the Cancer Drugs Fund as an option for treating relapsed or refractory DLBCL or PMBCL in adults after 2 or more systemic therapies[a]. NICE technology appraisal 567 (TA567) 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].

[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/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf

The technology

Lisocabtagene maraleucel (liso-cel, Celgene) is a chimeric antigen receptor (CAR) T-cell therapy that uses the patient's own healthy T-cells to fight the cancer by changing the patient's T-cells to target a protein called CD19. When lisocabtagene maraleucel binds to CD-19 expressing cells, the T-cell is activated to destroy the target cancer cell. It is administered as an intravenous infusion once only.

Lisocabtagene maraleucel does not currently have a marketing authorisation in the UK for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. It is being studied in 2 single-arm trials in people with DLBCL (de novo or transformed from FL) or with other aggressive B-cell malignancies (including PMBCL, HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, FL grade 3B, and MCL) after at least 2 lines of systemic therapy.

Intervention(s)	Lisocabtagene maraleucel
Population(s)	People with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma who have had at least 2 previous systemic treatments

Comparators	Established clinical management without lisocabtagene maraleucel, including but not limited to:
	• salvage chemotherapy combination regimens with or without rituximab, including:
	  ○ DHAP (dexamethasone, cytarabine, cisplatin)
	  ○ GDP (gemcitabine, dexamethasone, cisplatin)
	  ○ ICE (ifosfamide, carboplatin, etoposide)
	  ○ IVE (ifosfamide, epirubicin and etoposide)
	• rituximab monotherapy for people with relapsed stage 3 or 4 FL when all alternative treatment options have been exhausted
	• pixantrone monotherapy for people who are receiving third or fourth-line treatment, and have previously received rituximab
	• best supportive care (including radiotherapy)

Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response to treatment (including complete response and overall response) • 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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.
Other considerations	The availability and cost of biosimilar 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: 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 guidance 559. Review date February 2022 Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic

	therapies (2019) NICE technology appraisal guidance 567. Review date 2023 Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma (2014) NICE technology appraisal guidance 306. Review date to be confirmed Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (2008) NICE technology appraisal guidance 137. Last reviewed March 2011. Next review date to be confirmed Terminated appraisals Temsirolimus for the treatment of relapsed or refractory mantle cell lymphoma' (terminated appraisal) (2010). NICE Technology Appraisal 207. Appraisals in development (including suspended appraisals) Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576] NICE technology appraisal guidance. Publication date July 2020 Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma [ID986] NICE technology appraisal guidance. Suspended December 2012 'Lymphoma (mantle cell, relapsed, refractory) - lenalidomide' NICE technology appraisals guidance [ID739]. Suspended. 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. Related Quality Standards:

	Haematological cancers (2017) NICE quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2016) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017, Dec 2016. Domains 1, 2, 4 and 5. NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 29 - Blood and marrow transplantation services (adults and children) NHS England (2013) NHS standard contract for cancer: Chemotherapy (Adult) Section B part 1 Service specifications. Clinical Commissioning Policy. Reference B15/S/a.

References

1. World Health Organisation (2017) Classification of Tumours of Haematopoietic and Lymphoid Tissues

2. Rogers TS et al. (2019) High-grade B-Cell lymphoma with *MYC* and *BCL6* rearrangements associated with Richter transformation of chronic lymphocytic leukemia. Autopsy Case Reports 9(3): e2019090

3. Office of National Statistics (2018) Cancer Registration Statistics, England: first release, 2017. Accessed June 2020

4. Freedman A (2018) Follicular Lymphoma: 2018 Update on Diagnosis and Management. American Journal of Hematology 93(2): 296-305

5. 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

6. Mantle cell lymphoma. Cancer Research UK (using data from the Office for National Statistics and the regional cancer registries in Wales, Scotland and Northern Ireland using the latest data for 2017). Accessed July 2020

7. Diffuse large B-cell lymphoma. Lymphoma action. Accessed June 2020

8. Cancer Research UK (data collected in one area of England between 2004 and 2011). Accessed June 2020