NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of polatuzumab vedotin with rituximab and bendamustine within its marketing authorisation for treating adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable.

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 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 follicular lymphomas transform into high grade DLBCL (transformed high grade follicular lymphoma). 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 12,018 people diagnosed with NHL in England in 2016.[1] It is estimated that about 40% of people with NHL have DLBCL,[2] which would equate to 4,807 registrations of DLBCL per year.

Most people diagnosed with DLBCL are 65 or over.[3] Although most patients are cured with first-line chemotherapy, about 10-15% have primary refractory disease and a further 20-30% relapse.[4] Survival rates at 5 years for DLBCL are around 65-70% for stage I and II and around 50% at stages III and IV (patients diagnosed between 2004 and 2011).[5]

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 received previous treatment with rituximab and are in the third or fourth line of treatment.

The technology

Polatuzumab vedotin (brand name unknown, Roche Products) is an antibody drug conjugate that is, a monoclonal antibody combined with a cytotoxic agent called monomethyl auristatin E (MMAE). It acts by selectively binding to CD79b, a protein which is found on the surface of B-cells, resulting in the death of B-cells. It is administered as an intravenous infusion.

Polatuzumab vedotin does not currently have marketing authorisation in the UK for any indication. It has been studied in combination with rituximab and bendamustine in an ongoing randomized open-label clinical trial in adult patients with relapsed or refractory DLBCL. Polatuzumab vedotin in combination with rituximab and bendamustine was compared to rituximab and bendamustine.

Intervention(s)	Polatuzumab vedotin (with rituximab and bendamustine)
Population(s)	Adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable
Comparators	• Established clinical management without polatuzumab vedotin including but not limited to: ○ salvage chemotherapy with or without rituximab [DHAP (dexamethasone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide), IVE (ifosfamide, etoposide, epirubicin)], pixantrone monotherapy • 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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	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 TA306. Review date to be confirmed. 'Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma and after 2 or more systemic therapies' NICE technology appraisals guidance TA559 **Appraisals in development (including suspended appraisals)** 'Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma' NICE Technology Appraisal ID1166. Expected publication date March 2019

	'Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma' NICE technology appraisals guidance [ID986]. Suspended. Ibrutinib combination therapy for untreated diffuse large B-cell lymphoma NICE technology appraisals ID997 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 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 1-5

Questions for consultation

How do you define people for whom SCT is not suitable?

Have all relevant comparators for polatuzumab vedotin in people with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable been included in the scope? Is pixantrone an appropriate comparator? Which treatments are considered to be established clinical practice in the NHS for treating relapsed/refractory DLBCL?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Would you expect SCT to be feasible after treatment with polatuzumab vedotin in this population?

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

Where do you consider polatuzumab vedotin in combination with rituximab and bendamustine 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 polatuzumab vedotin in combination with rituximab and bendamustine 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 polatuzumab vedotin in combination with rituximab and bendamustine 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 polatuzumab vedotin in combination with rituximab and bendamustine 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. Office for National Statistics. Cancer registration statistics, England. 2019. Accessed February 2019
2. Cancer Research UK. Non-Hodgkin lymphoma 2018. Accessed February 2019
3. Lymphoma association Diffuse B-cell lymphoma Accessed February 2019
4. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. British journal of haematology. 2016;174(1):43-56. Available from: https://doi.org/10.1111/bjh.14136
5. Cancer Research UK Non-Hodgkin lymphoma- Survival Accessed February 2019

6. Office for National Statistics. Cancer survival in England - adults diagnosed. 2017. Accessed February 2019