NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib with rituximab for treating Waldenstrom's macroglobulinaemia ID1127

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib with rituximab within its marketing authorisation for treating Waldenstrom's macroglobulinaemia.

Background

Waldenstrom's macroglobulinaemia is a type of non-Hodgkin's lymphoma. Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Lymphomas are divided into two types: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Non-Hodgkin's lymphomas can be categorised according to their grade (how fast they grow) or cell type affected (B-cell or T-cell), as well as by their clinical features. Lymphoplasmacytic lymphomas are a group of rare low grade (slow growing or indolent) non-Hodgkin's lymphomas. The most common of these is Waldenstrom's macroglobulinaemia. Waldenstrom's macroglobulinaemia is caused by abnormal B cells which produce immunoglobulin M (IgM). IgM molecules are very large and can thicken the blood, reducing its flow through capillaries which can cause nerve damage in the hands and feet. Symptoms are highly variable, but the most common ones include severe fatigue, night sweats, lack of concentration, frequent/persistent infections, breathlessness, sinus problems, and unexplained weight loss.

Waldenstrom's macroglobulinaemia develops slowly and most people have no symptoms until they are diagnosed. As a result, most people are diagnosed in the advanced stages of the disease. Waldenstrom's macroglobulinaemia is more common in men and mainly affects people 70 years and older.[1] In 2016, there were 291 newly diagnosed cases of Waldenstrom's macroglobulinaemia registered in England.[2]

The British Committee for Standards in Haematology (BCSH) guidelines recommends treatment with a combination regimen with rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide). Chlorambucil monotherapy is also recommended for those people who cannot tolerate other treatments. Choice of treatment depends on a variety of clinical factors including grade of disease, kidney function, co-morbidities and whether a person is able to have stem cell transplantation. Patients treated with existing treatments generally have a partial response which lasts for a time before the disease relapses. Ibrutinib monotherapy is recommended for use in the Cancer Drugs Fund as

an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least one prior therapy (NICE technology appraisal 491).

The technology

Ibrutinib (Imbruvica, Janssen) is an inhibitor of a protein called Bruton's tyrosine kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.

Ibrutinib with rituximab does not currently have marketing authorisation in the UK for treating adult patients with Waldenstrom's macroglobulinaemia. It has been studied in a clinical trial in combination with rituximab, compared with placebo in combination with rituximab, in adults with Waldenstrom's macroglobulinaemia, who had not received previous treatment and in those with disease recurrence.

Ibrutinib has a marketing authorisation in the UK for treating adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or as first line treatment for patients in whom chemo-immunotherapy is unsuitable.

Intervention(s)	Ibrutinib with rituximab
Population(s)	Adults with Waldenstrom's macroglobulinaemia

Comparators	• Chemo-immunotherapy including the following treatments:
	  ○ rituximab and bendamustine
	  ○ rituximab, dexamethasone and cyclophosphamide
	  ○ rituximab and fludarabine with or without cyclophosphamide
	  ○ cladribine with or without rituximab
	• Rituximab only (for people in whom chemo-immunotherapy is not suitable)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • duration of response/remission • 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 patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If evidence allows the following subgroups will be considered. These include: • people who have received at least one prior therapy, and • people who have not received prior therapy 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: Ibrutinib for treating Waldenstrom's macroglobulinaemia (2017). NICE Technology Appraisal 491. Review date: when the data collection period has ended (expected to be September 2020) Related Guidelines: Haematological cancers: improving outcomes (2017). NICE guideline 47. Non-Hodgkin's lymphoma: diagnosis and management (2016). NICE guideline 52. Related NICE Pathways: Non-Hodgkin's lymphoma overview (2018) NICE Pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 105, Specialist Cancer services (adults). Department of Health and Social Care (2016) NHS

	Outcomes Framework 2016-2017. Domains 1 and 2. NHS England (2018) Specialised Services clinical commissioning policy: Bortezomib for Relapsed/ Refractory Waldenstrom's Macroglobulinaemia. Consultation.

Questions for consultation

Have all relevant comparators for ibrutinib with rituximab been included in the scope?

- Should haematopoietic stem cell transplantation be included as a comparator?
- Should ibrutinib alone be included as a comparator for groups it is recommended in the Cancer Drugs Fund?

Which treatments are considered to be established clinical practice in the NHS for Waldenstrom's macroglobulinaemia?

- For people who have not received prior therapy?
- For people with prior therapy? Would retreatment with primary therapy be considered?
- Should only people with symptomatic Waldenstrom's macroglobulinaemia be included in the population?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom ibrutinib with rituximab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ibrutinib with rituximab will fit into the existing Non-Hodgkin's lymphoma overview NICE Pathway?

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 ibrutinib with rituximab 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 ibrutinib with rituximab 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 ibrutinib with rituximab 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. Owen RG, Pratt G, Auer RL et al. (2014) Guidelines on the diagnosis and management of Waldenström macroglobulinaemia. British Journal of Haematology, 165:316-33. Accessed June 2018.

2. Office for National Statistics. (2018) Cancer Registration Statistics, England, 2016. Accessed June 2018.