NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Zanubrutinib for treating Waldenström's macroglobulinaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of zanubrutinib within its marketing authorisation for treating Waldenström's macroglobulinaemia.

Background

Waldenström'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 Waldenström's macroglobulinaemia.[1] Waldenström'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.[1,2] 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.

Waldenström's macroglobulinaemia is more common in men and mainly affects people 65 years and older.[3] Waldenström's macroglobulinaemia is incurable and the median life expectancy is 5 years.[2] In 2017, there were 353 newly diagnosed cases of Waldenström's macroglobulinaemia registered in England.[4] In 2018-19, there were a total of 5,384 hospital episodes with a primary diagnosis of Waldenström's macroglobulinaemia in England.[5]

There is no established standard of care for Waldenström's macroglobulinaemia in England. The British Committee for Standards in Haematology (BCSH) guidelines recommend treatment with a combination regimen with rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide).[2] Chlorambucil monotherapy is also recommended for those people who cannot tolerate other treatments. Choice of treatment usually 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.[2] Patients treated with existing treatments generally have a partial response which lasts for a time before the disease relapses. More recently, mutations in the MYD88 gene have been found to confer a better prognosis and greater response to Bruton's tyrosine kinase (BTK) inhibitors. Around 90% of people with Waldenström's macroglobulinaemia have a MYD88 mutation.[6]

Ibrutinib monotherapy is recommended for use in the Cancer Drugs Fund as an option for treating Waldenström's macroglobulinaemia in adults who have had at least one prior therapy (NICE technology appraisal 491).

The technology

Zanubrutinib (brand name unknown, BeiGene) is a BTK inhibitor which inhibits B-cell proliferation and promotes cell death. It is administered orally.

Zanubrutinib does not currently have a marketing authorisation in the UK for any indication. It has been studied in a clinical trial in patients with Waldenström's macroglobulinaemia with or without MYD88 mutation, compared with ibrutinib.

Intervention(s)	Zanubrutinib
Population(s)	Adults with Waldenström's macroglobulinaemia

Comparators	Treatment without zanubrutinib:
	For people who are eligible for chemo-immunotherapy:
	• chemo-immunotherapy including the following treatments:
	  • rituximab and bendamustine (BR)
	  • dexamethasone, rituximab and cyclophosphamide (DRC)
	  • fludarabine and rituximab (FR)
	  • fludarabine, cyclophosphamide and rituximab (FCR)
	  • cladribine and rituximab (Clad-R)
	  • cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab
	• ibrutinib in people who have had at least 1 prior therapy.
	For people who are not eligible for chemo-immunotherapy:
	• chlorambucil, with or without rituximab
	• rituximab monotherapy
	• ibrutinib in people who have had at least 1 prior therapy
	• best supportive care.

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • time to next treatment • 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. 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 patient access schemes for the intervention or comparator technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for MYD88 in people with Waldenström's macroglobulinaemia who would not otherwise have been tested, if appropriate. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals'.
Other considerations	If the evidence allows the following subgroups will be considered: • people with MYD88 mutation-positive Waldenström's macroglobulinaemia • people who have received at least 1 prior therapy, and • people who have not received prior therapy. The availability and cost of biosimilars 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:** Ibrutinib for treating Waldenstrom's macroglobulinaemia (2017) NICE technology appraisal guidance 491. Review date: when the data collection period has ended (expected to be September 2020) **Terminated appraisals:** Ibrutinib with rituximab for treating Waldenstrom's

	macroglobulinaemia (2019) NICE technology appraisal 608 **Related Guidelines:** Haematological cancers: improving outcomes (2017). NICE guideline 47 Non-Hodgkin's lymphoma: diagnosis and management (2016) NICE guideline 52 **Related Quality Standards:** Haematological cancers (2017) NICE quality standard 150 **Related NICE pathways:** Non-Hodgkin's lymphoma overview (2018) 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: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England (2018/2019) Manual for prescribed specialised services 2018/19 Chapter 105: Specialist cancer services (adults) NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a NHS England. 2013/2014 NHS Standard Contract for Cancer. Radiotherapy (All Ages). B01/S/a. NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a. Department of Health (2016) NHS outcomes framework 2016 to 2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2018) Specialised Services clinical commissioning policy: Bortezomib for Relapsed/ Refractory Waldenstrom's Macroglobulinaemia. Consultation NHS England (2017) Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) for lymphoplasmacytic lymphoma (adults). 16067/P

Questions for consultation

Is zanubrutinib intended to be offered to people who have not received previous treatment for Waldenström's macroglobulinaemia and are considered suitable candidates for standard chemo-immunotherapy?

Have all relevant comparators for zanubrutinib been included in the scope? In particular:

- Which treatments are considered to be established clinical practice in the NHS for Waldenström's macroglobulinaemia?
- Should alemtuzumab included as a comparator?
- Should bortezomib be included as a comparator?
- How should best supportive care be defined?

Are the outcomes listed appropriate?

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

Where do you consider zanubrutinib 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 zanubrutinib 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 zanubrutinib 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 zanubrutinib 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. Lymphoma Action. Lymphoplasmacytic lymphoma and Waldenström's macroglobulinaemia. Accessed May 2020.
2. Owen, R et al. (2014) Guidelines on the diagnosis and management of Waldenström macroglobulinaemia. British Journal of Haematology, 165:316-33.
3. WMUK. (2018) What is WM? Accessed April 2020
4. Office of National Statistics (2019), Cancer Statistics Registrations, England, 2017 dataset. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland
5. NHS Digital (2019) Hospital Admitted Patient Care Activity 2018-19. Accessed July 2020
6. Baron, M et al. (2019) How Recent Advances in Biology of Waldenström's Macroglobulinemia May Affect Therapy Strategy. Current Oncology Reports, 21:27