NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib with obinutuzumab within its marketing authorisation for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma.

Background

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, unexplained weight loss and increased susceptibility to infection. People with CLL may live with a considerable burden of symptoms impacting on their quality of life, whether or not they have received treatment. Small lymphocytic lymphoma (SLL) is a different form of the same disease, where SLL cells are found in organs and tissues of the lymphatic system.

In England there were 3,252 new cases of CLL in 2015[1]. The risk of developing CLL increases with age and is more common in men[1].

CLL and SLL are treated in the same way. Treatment options vary depending on factors such as stage of disease, performance status and co-morbidities. Some people may not need treatment when they first receive a diagnosis, if they don't have any symptoms. When immediate treatment is needed, fludarabine combination therapy is the standard of care for people with untreated CLL or SLL. NICE technology appraisal 174 recommends rituximab in combination with fludarabine and cyclophosphamide (FCR) as a first-line treatment option for people with untreated CLL. Fludarabine combination therapy may not be suitable for some people, for example, people who have comorbidities such as impaired renal function, hypertension or diabetes. NICE technology appraisal 216 recommends bendamustine as a first-line treatment of chronic lymphocytic leukaemia for people who cannot have fludarabine. Obinutuzumab with chlorambucil (NICE technology appraisal 343), or ofatumumab with chlorambucil (NICE technology appraisal 344) are recommended as treatment options when fludarabine-based therapy and bendamustine-based therapy are not suitable. The British Committee for Standards in Haematology also recommends chlorambucil with or without rituximab[2].

Identified genetic changes such as deletions or mutations can influence treatment choice. For untreated CLL with a 17p deletion or TP53 mutation,

NICE technology appraisals 359 and 429 recommend idelalisib with rituximab, and ibrutinib alone (for people for whom chemo-immunotherapy is unsuitable).

NICE technology appraisal guidance 487 recommends venetoclax for use in the Cancer Drugs Fund for people with untreated CLL with a 17p deletion or TP53 mutation for whom B-cell receptor pathway inhibitors are unsuitable.

The technology

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

Ibrutinib has a marketing authorisation in the UK for untreated CLL alone but does not currently have a marketing authorisation in the UK for use with obinutuzumab in untreated CLL or SLL. It is being studied in a clinical trial with obinutuzumab compared with chlorambucil with obinutuzumab for untreated CLL or SLL in adults who are over 65 years or if under 65 years must have disease with a 17p deletion or TP53 mutation, a Cumulative Illness Ration Score above 6 or a creatinine clearance of less than 70 ml/min.

Intervention(s)	Ibrutinib with obinutuzumab
Population(s)	People with untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma
Comparators	• Rituximab with fludarabine and cyclophosphamide • Chlorambucil with or without rituximab (for people for whom fludarabine-based therapy is unsuitable) • Bendamustine (for people for whom fludarabine-based therapy is unsuitable) • Obinutuzumab with chlorambucil (for people for whom fludarabine-based therapy and bendamustine is unsuitable) • Ofatumumab with chlorambucil (for people for whom fludarabine-based therapy and bendamustine is unsuitable) For CLL with a 17p deletion or TP53 mutation: • Ibrutinib alone (for people for whom chemo-immunotherapy is unsuitable) • Idelalisib with rituximab

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. 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 and cost of biosimilar products should be taken into account. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
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: Venetoclax for treating chronic lymphocytic leukaemia (2017) NICE technology appraisal 487. To be updated when the data collection period has ended (expected December 2020). Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017) NICE

	technology appraisal 429. Review date January 2020. Idelalisib for treating chronic lymphocytic leukaemia (2015) NICE technology appraisal 359. Review date September 2018. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal 344. Review date June 2018. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal 343. Review date June 2018. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011) NICE technology appraisal 216. On static list. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal 174. On static list. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (2007). NICE technology appraisal 119. On static list. Terminated appraisals: Ofatumumab with chemotherapy for treating chronic lymphocytic leukaemia (terminated appraisal) (2017). NICE technology appraisal 470. Idelalisib with ofatumumab for treating chronic lymphocytic leukaemia (terminated appraisal) (2017). NICE technology appraisal 469. Ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal) (2017). NICE technology appraisal 452. Appraisals in development (including suspended appraisals): Venetoclax with ibrutinib and obinutuzumab for untreated chronic lymphocytic leukaemia NICE technology appraisals guidance ID1270. Publication date to be confirmed. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia Proposed NICE technology

	appraisal ID1402. Publication date to be confirmed. Related guidelines: Haematological cancers: improving outcomes (2016). NICE guideline 47 Review date to be confirmed. Related quality standards: Haematological cancers (2017). NICE quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2017) NICE pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 105. Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1.

Questions for consultation

Have all relevant comparators for ibrutinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma?

Are the outcomes listed appropriate?

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

Where do you consider ibrutinib 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 ibrutinib 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 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 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 https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/process).

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 comparators still clinically relevant?

- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Cancer Research UK (2015) Chronic lymphocytic leukaemia incidence statistics [online; accessed May 2018]

2. Follows G, Bloor A, Dearden C et al. (2015) Interim statement from the BCSH CLL Guidelines Panel [online; accessed May 2018]