**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal**

# Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

**Draft scope (post-referral)**

## Final remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib within its licensed indication for chronic lymphocytic leukaemia.

## Background

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, weight loss and increased susceptibility to infection. CLL is the most common form of leukaemia.

In England around 2,700 people were diagnosed with CLL in 2011.[1] The risk of developing CLL increases with age and is more common in men. Median survival ranges from about 3 to over 10 years depending on the genetic subtype and the stage at which the disease is diagnosed.[2]

Approximately 5% to 10% of people diagnosed with CLL are considered to have 'high-risk' disease characterised by the presence of cytogenetic mutations or abnormalities (that is, 17p deletion or TP53 mutation).[3] The presence of 17p deletion or TP53 mutation influences the rate of cell growth as well as the resistance of the disease to treatment. People with the 17p deletion or TP53 mutation have a median survival of 2 to 3 years.[3]

Treatment options vary depending on factors such as stage of CLL, performance status and co-morbidities. The appraisal includes 2 groups of people with CLL:

- People who have received at least 1 therapy; and
- People with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable.

Chemo-immunotherapy is a combination of chemotherapy medicines and treatments that stimulate the immune system to kill cancer cells.

For **people who have received at least 1 therapy**, treatment options include fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine with or without rituximab, chlorambucil with or without rituximab and idelalisib.

- NICE technology appraisal guidance 193 recommends FCR as an option for people with relapsed or refractory CLL unless the disease is refractory to fludarabine or has been previously treated with rituximab.

- Bendamustine does not have a UK marketing authorisation for previously treated CLL, but it is used with or without rituximab in clinical practice in England through the Cancer Drugs Fund.

- Chlorambucil has a UK marketing authorisation for CLL and is used in clinical practice, with or without rituximab, in relapsed or refractory CLL where FCR is unsuitable.

- Idelalisib in combination with rituximab is the subject of an ongoing NICE technology appraisal, and is funded by the Cancer Drugs Fund for relapsed or refractory CLL.

There are limited treatment options for **people with untreated CLL associated with 17p deletion or TP53 mutation** for whom chemo-immunotherapy is not suitable.

- Alemtuzumab does not have a marketing authorisation for CLL in the European Union because its marketing authorisation for this indication was withdrawn at the request of the company for commercial reasons. However alemtuzumab is currently available in England through a patient access programme agreed by the company and the European Medicines Agency.

- Idelalisib in combination with rituximab has a UK marketing authorisation for this indication and is the subject of an ongoing NICE technology appraisal. Idelalisib is not funded by the Cancer Drugs Fund for untreated CLL.

**The technology**

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

Ibrutinib has a marketing authorisation in the UK for treating adult patients with CLL 'who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy'.

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| **Intervention(s)** | • Ibrutinib |
| **Population(s)** | • Adults with chronic lymphocytic leukaemia who have received at least 1 therapy<br>• Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable |

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| **Comparators** | For adults with chronic lymphocytic leukaemia who have received at least 1 prior therapy:<br>• Fludarabine in combination with cyclophosphamide and rituximab<br>• Bendamustine (with or without rituximab) [not licensed in the UK for this indication, funded by the CDF]<br>• Chlorambucil (with or without rituximab)<br>• Corticosteroids (with or without rituximab)<br>• Idelalisib in combination with rituximab (NICE guidance is in development, funded by the CDF in the interim)<br>• Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support).<br><br>For adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable:<br>• Alemtuzumab with or without corticosteroids<br>• Idelalisib in combination with rituximab (subject to ongoing NICE technology appraisal, *not* funded by the CDF in the interim)<br>• Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support). |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life. |

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| **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.<br><br>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.<br><br>Costs will be considered from an NHS and Personal Social Services perspective.<br><br>If appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices.<br><br>The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.<br><br>Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in economic analyses, rather than the list price. |
| **Other considerations** | If the evidence allows, the following subgroups will be considered for adults with chronic lymphocytic leukaemia who have received at least 1 prior therapy:<br><br>• Presence or absence of 17p deletion.<br>• Presence or absence of TP53 mutation.<br><br>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 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:<br><br>Technology Appraisal No. 202, October 2010, 'Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab'. Review Proposal Date TBC.<br><br>Technology Appraisal No. 193, July 2010, 'Rituximab for the treatment of relapsed chronic lymphocytic leukamia'. Moved to the static list, March 2014.<br><br>Appraisals in development:<br><br>Idelalisib for treating chronic lymphocytic leukaemia. NICE technology appraisals guidance. ID764. |

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| | Publication expected October 2015.<br><br>Proposed appraisal: Idelalisib in combination with ofatumumab for chronic lymphocytic leukaemia. Proposed NICE technology appraisal ID 817. Publication date to be confirmed.<br><br>Related Guidelines:<br><br>NICE cancer service guidance (2003). Improving outcomes in haematological cancers.<br><br>Related NICE Pathways:<br><br>NICE pathway on blood and bone marrow cancers, available at:<br><br>http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers |
| **Related National Policy** | National service framework: 'Improving outcomes: a strategy for cancer', Jan 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/135516/dh_123394.pdf.pdf<br><br>NHS England Manual for prescribed specialised services 2013/2014. Specialist cancer services (adults) [section 105, page 234]: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf<br><br>NHS England 2013/14 NHS standard contract for cancer: chemotherapy (adult). Section B part 1- service specifications: http://www.england.nhs.uk/wp-content/uploads/2013/06/b15-cancr-chemoth.pdf<br><br>Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf |

**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 CLL?
- Is rituximab monotherapy part of established clinical practice in the NHS for CLL?
- Are any of the following treatments part of established clinical practice in the NHS for previously untreated CLL associated with 17p deletion or TP53 mutation?
    - Bendamustine (with or without rituximab)
    - Chlorambucil (with or without rituximab)
    - Ofatumumab in combination with bendamustine or chlorambucil

    - Obinutuzumab in combination with chlorambucil
- Is best supportive care defined appropriately in the scope?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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 on 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 is 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.

**References**

1. Cancer Research UK (2015). Chronic lymphocytic leukaemia (CLL) incidence statistics. Accessed June 2015.

2. Cancer Research UK (2015). Statistics and outlook for chronic lymphocytic leukaemia. Accessed June 2015.

3. Eichhorst B, Dreyling M, Robak T et al. on behalf of the European Society for Medical Oncology (ESMO) Guidelines Working Group (2011). Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 22 (S6): vi50–vi54.