NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib with rituximab for untreated chronic lymphocytic leukaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib with rituximab within its marketing authorisation for untreated 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. People with CLL may live with a considerable burden of symptoms impacting on their quality of life, whether or not they have received treatment.

In England there were 3,157 new cases of CLL in 2017[1]. The risk of developing CLL increases with age and is more common in men[1].

Treatment options for untreated CLL depend on factors such as stage of disease, performance status and co-morbidities. Most people will not have symptoms when they first receive a diagnosis and will not need any treatment, if they don't have any symptoms. 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)[2]. The presence of 17p deletion or TP53 mutation can increase both the rate of cell growth and the resistance of the disease to treatment.

Treatment choices are influenced by the presence of biological markers such as 17p deletion or TP53 mutation. People with untreated CLL and 17p deletion or TP53 mutation may receive idelalisib with rituximab (NICE technology appraisal guidance 359) or ibrutinib alone (NICE technology appraisal guidance 429) if chemo-immunotherapy is unsuitable. For people whom B-cell receptor pathway inhibitors are unsuitable they may receive venetoclax through the Cancer Drugs Fund (NICE technology appraisal guidance 487*.

NICE technology appraisal 174 recommends rituximab with fludarabine and cyclophosphamide (FCR) for people without a 17p deletion or TP53 mutation

* Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf

when fludarabine in combination with cyclophosphamide is considered appropriate. People who cannot have FCR therapy may receive bendamustine with or without rituximab (NICE technology appraisal guidance 216) and people for whom fludarabine-based therapy and bendamustine is unsuitable may receive obinutuzumab with chlorambucil (NICE technology guidance 343). NICE technology guidance 343 also states that people who cannot have fludarabine combination chemotherapy may receive chlorambucil, with or without, rituximab.

The technology

Ibrutinib (Imbruvica, Janssen-Cilag) is a small-molecule inhibitor of a protein called Bruton's tyrosine kinase (BTK), which stops B-cell (lymphocyte) proliferation and promotes cell death. It is administered orally.

Rituximab is a chimeric (mouse/human) genetically engineered monoclonal antibody. It targets the CD-20 surface marker of normal and malignant B-cell lymphocytes. It is administered by intravenous infusion.

Ibrutinib as monotherapy or with obinutuzumab has a market authorisation in the UK for treating adults with previously untreated chronic lymphocytic leukaemia (CLL). Ibrutinib as monotherapy or with bendamustine and rituximab has a UK marketing authorisation for treating adults with CLL who have received at least one prior therapy. It does not currently have a marketing authorisation in the UK for untreated CLL. It is being studied in a clinical trial in combination with rituximab compared with fludarabine phosphate, cyclophosphamide, and rituximab (FCR) in adults with untreated CLL or small lymphocytic lymphoma.

Intervention(s)	Ibrutinib with rituximab
Population(s)	People with untreated chronic lymphocytic leukaemia
Comparators	Without a 17p deletion or TP53 mutation: • fludarabine, cyclophosphamide and rituximab (FCR) • bendamustine with or without rituximab (BR), for people for whom fludarabine-based therapy is unsuitable • chlorambucil with or without rituximab, for people for whom fludarabine-based therapy is unsuitable • obinutuzumab with chlorambucil, for people for whom fludarabine-based therapy and bendamustine is unsuitable. 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 rate • 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 and cost of biosimilar products of should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • people with untreated CLL with 17p deletion or TP53 mutation • people with untreated CLL for whom fludarabine-based therapy is unsuitable • people with untreated CLL for whom bendamustine-based therapy is unsuitable. 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 CDF data collection period has ended (expected December 2020). Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal 343. On static list 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: 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. Suspended. Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma. NICE technology appraisals guidance ID1375. Suspended. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. NICE technology appraisals guidance ID1402. Publication date to be confirmed. Acalabrutinib for treating chronic lymphocytic leukaemia. NICE technology appraisals guidance ID1613. 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 Pathway: Blood and bone marrow cancers
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 (2016) NHS Outcomes Framework 2016 to 2017: Domain 1.

Questions for consultation

Have all relevant comparators for ibrutinib with rituximab for untreated chronic lymphocytic leukaemia been included in the scope?

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 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 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. Cancer registration statistics, England: 2017 (2019). Office for National Statistics. Accessed February 2020.
2. Eichhorst B, Robak T, Montserrat E et al. on behalf of the European Society for Medical Oncology (ESMO) Guidelines Committee (2015). Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (S5): v78-v84. With eUpdate (2017).

