NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia

Draft scope

Draft remit/appraisal objective

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

Background

Chronic lymphocytic leukaemia (CLL) is the most common type of chronic leukaemia and is a type of cancer that affects the white blood cells. It tends to progress slowly over many years. CLL mostly affects people 60 years of age and over and is rare in people 40 years of age and younger. In England there were 4,226 new cases of CLL in 2017. The risk of developing CLL increases with age and is more common in men[1].

In CLL, the material found inside some bones (bone marrow) produces too many white blood cells called lymphocytes that aren't fully developed and don't work properly. Over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising[2]. People with CLL may live with a considerable burden of symptoms impacting on their quality of life, whether or not they have received treatment. 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, a 17p deletion or TP53 mutation)[3]. The presence of a 17p deletion or TP53 mutation can increase both the rate of cell growth and the resistance of the disease to treatment. The presence of an immunoglobulin heavy chain gene (IgHV) mutation may also affect clinical outcomes.

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. Table 1 below summarises the treatment options which are currently available as routine practice in the NHS in England for untreated CLL.

Table 1. Treatment options for untreated CLL in NHS practice

NICE technology appraisal	*Treatment option for untreated CLL*	*Population*
People without a 17p deletion (del[17p]) or TP53 mutation		
TA174	rituximab with fludarabine and cyclophosphamide (FCR)	people for whom fludarabine in combination with cyclophosphamide is considered appropriate
TA216	bendamustine with or without rituximab (BR)	people for whom fludarabine combination chemotherapy is

		not appropriate
TA343	obinutuzumab with chlorambucil	people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable
TA689	acalabrutinib	
TA663	venetoclax with obinutuzumab	
TA663 – Cancer Drugs Fund	venetoclax with obinutuzumab	people for whom fludarabine-based therapy or bendamustine-based therapy is suitable
TA487 – Cancer Drugs Fund	venetoclax	people whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor
People with a del(17p) or TP53 mutation		
TA359	idelalisib with rituximab	people with a del(17p) or TP53 mutation
TA689	acalabrutinib	
TA663	venetoclax with obinutuzumab	
TA429	ibrutinib monotherapy	people for whom chemo-immunotherapy is unsuitable
TA487 – Cancer Drugs Fund	venetoclax	when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor

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.

Venetoclax is a selective blocker of B-cell lymphoma-2 (BCL-2), which is a protein that allows cancer cells to stay alive. Venetoclax is administered orally.

Ibrutinib as monotherapy or with obinutuzumab or rituximab has a marketing authorisation in the UK for treating adults with previously untreated CLL. Ibrutinib as monotherapy or with bendamustine and rituximab has a marketing authorisation in the UK for treating adults with CLL who have received at least one prior therapy.

Ibrutinib with venetoclax does not currently have a marketing authorisation in the UK for untreated CLL. It is being studied in a clinical trial compared with chlorambucil plus obinutuzumab in adults with untreated CLL or small lymphocytic lymphoma.

Intervention(s)	Ibrutinib with venetoclax
Population(s)	People with untreated chronic lymphocytic leukaemia

Comparators	For people 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 • obinutuzumab with chlorambucil, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • acalabrutinib, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • venetoclax plus obinutuzumab, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable For people with a 17p deletion or TP53 mutation: • acalabrutinib • venetoclax plus obinutuzumab • 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 and generic products 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 a 17p deletion or TP53 mutation • according to IgHV mutation status (mutated or unmutated) • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable. The availability and cost of biosimilar and generic products 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: Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (2021). NICE technology appraisal 689 Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2020). NICE technology appraisal 663. 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). Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017). NICE technology appraisal guidance 429 Idelalisib for treating chronic lymphocytic leukaemia (2015). NICE technology appraisal guidance 359 Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015). NICE technology appraisal 343. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011). NICE technology appraisal 216. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal 174. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (2007). NICE technology appraisal 119.

	Terminated appraisals: Ibrutinib with rituximab for untreated chronic lymphocytic leukaemia (terminated appraisal) (2021). NICE technology appraisal 703 Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (terminated appraisal) (2021). NICE technology appraisal 702. Ofatumumab with chemotherapy for treating chronic lymphocytic leukaemia (2017) NICE technology appraisal 470 (terminated appraisal: Novartis has discontinued ofatumumab) 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. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal 344 (terminated appraisal: Novartis has discontinued ofatumumab) Appraisals in development (including suspended appraisals): Venetoclax with ibrutinib and obinutuzumab for untreated chronic lymphocytic leukaemia. NICE technology appraisals guidance ID1270. Suspended. 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
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 venetoclax 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 venetoclax is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ibrutinib with venetoclax 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 venetoclax 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 venetoclax 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 venetoclax 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 July 2021.
2. Chronic lymphocytic leukaemia. NHS Choices. accessed July 2021
3. 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.

