NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Zanubrutinib for untreated chronic lymphocytic leukaemia

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of zanubrutinib within its marketing authorisation for treating untreated chronic lymphocytic leukaemia.

Background

Chronic lymphocytic leukaemia (CLL) is the most common form of chronic leukaemia and is a type of cancer that affects the white blood cells. It tends to progress slowly over many years. The risk of developing CLL increases with age and is more common in men. CLL mostly affects people 60 years of age and over and is rare in people 40 years of age and younger.[1-3] Around 3,800 people are diagnosed with CLL in the UK each year.[2]

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 anaemia, swollen lymph nodes, spleen enlargement, unexplained weight loss and increased susceptibility to infection.[1] People with CLL may live with a considerable burden of symptoms impacting on their quality of life whether or not they have received treatment.

The British Society of Haematology (BSH) defines people with 'high risk' CLL as those with previously untreated CLL associated with a 17p deletion or TP53 mutation (the presence of 17p deletion or TP53 mutation influences the rate of cell growth as well as the resistance of the disease to treatment).[4] The presence of 17p deletion or TP53 mutation can be used as markers to predict the prognosis of people with CLL. The presence of an immunoglobulin heavy chain gene (IgHV) mutation may also affect clinical outcomes.[5]

Treatment of untreated CLL is complex and depends on several factors such as stage of disease, previous treatment, patient's age, symptoms, and general state of health. 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. Chemotherapy can achieve complete remission, but people may eventually relapse. Immunotherapies, such as rituximab and obinutuzumab, have been shown to improve survival and remission rates, particularly when combined with chemotherapy in chemoimmunotherapy regimens. Targeted therapies, such as ibrutinib, idelalisib and venetoclax are particularly useful in people with 17p deletion or TP53 mutation.[6]

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	***Date***	***Treatment option for untreated CLL***	***Population***
People without a 17p deletion (del[17p]) or TP53 mutation			
TA689	April 2021	acalabrutinib	people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable
TA663	December 2020	venetoclax and obinutuzumab	
TA343	June 2015	obinutuzumab with chlorambucil*	
TA216	February 2011	bendamustine with or without rituximab (BR)*	people for whom fludarabine combination chemotherapy is not appropriate
TA174	July 2009	rituximab with fludarabine and cyclophosphamide (FCR)	people for whom fludarabine in combination with cyclophosphamide is considered appropriate
People with a del(17p) or TP53 mutation			
TA796	June 2022	venetoclax	people for whom a B-cell receptor pathway inhibitor is unsuitable
TA689	April 2021	acalabrutinib	-
TA663	December 2020	venetoclax and obinutuzumab	-
TA429	January 2017	ibrutinib monotherapy	people for whom chemo-immunotherapy is unsuitable
TA359	October 2015	idelalisib with rituximab	people who are not eligible for any other therapies
TA343	June 2015	obinutuzumab with chlorambucil*	people for whom fludarabine -based therapy or bendamustine-based therapy is unsuitable
TA216	February 2011	bendamustine with or without rituximab (BR)*	people for whom fludarabine combination chemotherapy is not appropriate
TA174	July 2009	rituximab with fludarabine and cyclophosphamide (FCR)	people for whom fludarabine in combination with cyclophosphamide is considered appropriate

*Bendamustine or chlorambucil-based chemo-immunotherapy are no longer recommended by British Society of Haematology.[4]

The technology

Zanubrutinib (Brukinsa, Beigene) does not currently have a marketing authorisation in the UK for untreated chronic lymphocytic leukaemia. It has been studied in a clinical trial compared with bendamustine plus rituximab in adults with untreated CLL.

Intervention(s)	Zanubrutinib
Population(s)	People with untreated chronic lymphocytic leukaemia
Subgroups	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

Comparators	For people without a 17p deletion or TP53 mutation, established clinical management without zanubrutinib, including (but not limited to): • fludarabine, cyclophosphamide and rituximab • acalabrutinib, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • bendamustine with or without rituximab, for people for whom fludarabine combination chemotherapy is not appropriate • obinutuzumab with chlorambucil, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • venetoclax and obinutuzumab, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860] (subject to NICE evaluation) For people with a 17p deletion or TP53 mutation, established clinical management without zanubrutinib, including (but not limited to): • acalabrutinib • venetoclax and obinutuzumab • venetoclax, for people for whom a B-cell receptor pathway inhibitor is unsuitable • ibrutinib, for people for whom chemo-immunotherapy is unsuitable • idelalisib with rituximab , for people who are not eligible for any other therapies • fludarabine, cyclophosphamide and rituximab • bendamustine with or without rituximab, for people for whom fludarabine combination chemotherapy is not appropriate • obinutuzumab with chlorambucil, for people for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable • ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860] (subject to NICE evaluation)

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. 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should 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	**Related Technology Appraisals:** Venetoclax for treating chronic lymphocytic leukaemia (2022). NICE Technology appraisal guidance 796. Review date 2025. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (2021). NICE technology appraisal 689. Review date 2024 Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2020). NICE technology appraisal 663. Review date 2023

	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. **Related appraisals in development:** Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance [ID3860]. Publication expected March 2023. Acalabrutinib with venetoclax and obinutuzumab for untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance [TS ID 11768]. Publication date TBC **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 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

Questions for consultation

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

Are bendamustine or chlorambucil-based chemo-immunotherapy regimens currently used in NHS clinical practice for previously untreated CLL?

Are the outcomes listed appropriate?

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

Where do you consider zanubritinib will fit into the existing treatment pathway for untreated chronic lymphocytic leukaemia?

Would zanubrutinib be a candidate for managed access?

Do you consider zanubritinib 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 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 committee to take account of these benefits.

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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

NICE's health technology evaluations: the manual 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. Chronic lymphocytic leukaemia (2019) NHS Choices. Accessed July 2022

2. Chronic lymphocytic leukaemia (CLL) incidence statistics (2018) Cancer Research UK. Accessed July 2022

3. What is chronic lymphocytic leukaemia (CLL)? (2021). Cancer Research UK. Accessed July 2022

4. Walewska R, Parry-Jones N, Eyre TA et al. (2022) Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology. 197 (5), 544-557

5. Eichhorst B, Robat T, Montserrat E et al. (2020). Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up on behalf of the ESMO Guidelines Committee. *Annals of Oncology*. 32 (1), 23-33

6. Chronic lymphocytic leukaemia: management approach (2022) BMJ Best Practice. Accessed July 2022