NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Zanubrutinib for treating chronic lymphocytic leukaemia

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of zanubrutinib within its marketing authorisation for treating 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. CLL usually progresses slowly, but over time people can develop anaemia, swollen lymph nodes, spleen enlargement and unexplained weight loss. People with CLL may live with a considerable burden of symptoms and an increased susceptibility to infection impacting on their quality of life, whether or not they have had treatment.[1]

The British Society of Haematology 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 and is associated with resistance of the disease to conventional chemotherapy treatments.[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 CLL is complex and depends on several factors such as stage of disease, previous treatment, patient's age, symptoms, and general state of health. Many people with CLL will not have symptoms when they are first diagnosed and will have a period of active surveillance. The disease is monitored for progression and treatment is initiated upon progression. Chemotherapy can achieve complete remission, but the disease may eventually relapse. Immunotherapies, such as rituximab, have been shown to improve survival and remission rates, particularly when combined with chemotherapy. Targeted therapies, such as acalabrutinib, ibrutinib, idelalisib and venetoclax are particularly useful in people with a poor prognosis, such as those with relapsed or refractory disease, and those with 17p deletion or TP53 mutation.[6]

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 or TP53 mutation			
TA689	April 2021	acalabrutinib	for whom fludarabine plus cyclophosphamide and rituximab, or bendamustine plus rituximab is unsuitable
TA343	June 2015	obinutuzumab with chlorambucil	for whom fludarabine-based therapy and bendamustine-based therapy is unsuitable
TA216	February 2011	bendamustine with or without rituximab	for those who cannot have fludarabine combination chemotherapy
No TA published*	N/A	chlorambucil, with or without rituximab	
TA174	July 2009	rituximab with fludarabine and cyclophosphamide	for whom fludarabine in combination with cyclophosphamide is considered appropriate
People with a 17p deletion or TP53 mutation			
TA689	April 2021	acalabrutinib	for those with a 17p deletion or TP53 mutation
TA429	January 2017	ibrutinib monotherapy	for whom chemo-immunotherapy is unsuitable
TA359	October 2015	idelalisib with rituximab	for those with a 17p deletion or TP53 mutation
*use of chlorambucil, with or without rituximab, is detailed in TA343.			

Table 2. Treatment options for relapsed or refractory CLL in NHS practice

NICE technology appraisal	***Date***	***Treatment option for relapsed or refractory CLL***	***Population***
TA796	June 2022	venetoclax	• people with a 17p deletion or TP53 mutation whose disease has progressed after a B-cell receptor pathway inhibitor or • people without a 17p deletion or TP53 mutation whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor

TA689	April 2021	acalabrutinib	previously treated CLL in adults
TA561	February 2019	venetoclax with rituximab	people who have had at least 1 previous therapy
TA429	January 2017	ibrutinib	
TA359	October 2015	idelalisib with rituximab	people whose disease has been treated but has relapsed within 24 months
TA193	July 2010	rituximab in combination with fludarabine and cyclophosphamide	people with relapsed or refractory CLL except when the condition: • is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or • has previously been treated with rituximab, unless: - in the context of a clinical trial, at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or - in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide
TA29	September 2001	fludarabine	people who have had to stop their first chemotherapy treatment

The technology

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

Intervention	Zanubrutinib
Population	People with chronic lymphocytic leukaemia

Subgroups	If the evidence allows the following subgroups will be considered: • untreated CLL • relapsed or refractory CLL Within untreated CLL, if the evidence allows the following subgroups may be considered: • people for whom fludarabine-based therapy is suitable • people for whom fludarabine-based therapy is unsuitable • people for whom fludarabine-based and bendamustine-based therapy are unsuitable • people with a 17p deletion or TP53 mutation
Comparators	**For untreated CLL, including (but not limited to):** • acalabrutinib (17p deletion or TP53 mutation or if fludarabine or bendamustine based regimens are not suitable) • ibrutinib (17p deletion or TP53 mutation) • ibrutinib with venetoclax (subject to ongoing NICE appraisal) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab • fludarabine, cyclophosphamide and rituximab • venetoclax with obinutuzumab • venetoclax (17p deletion or TP53 mutation and if B-cell receptor pathway inhibitor is unsuitable) **For relapsed or refractory CLL, including (but not limited to):** • acalabrutinib • ibrutinib • venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • venetoclax with rituximab • idelalisib with rituximab

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • time to treatment failure • 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 treating chronic lymphocytic leukaemia (2021). NICE Technology appraisal guidance 689. Review date 2024 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (2019). NICE technology appraisal guidance TA561. Review date 2022

	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. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (2010). NICE Technology appraisal guidance 193. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (2001). NICE Technology appraisal guidance 29. **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

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