NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (Managed access partial review of TA663)

Final scope

Final remit/evaluation objective

To appraise the clinical and cost effectiveness of venetoclax with obinutuzumab within its marketing authorisation for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) is suitable.

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 4,000 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 are not fully developed and do not 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, person'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 may be particularly useful in people with a poor prognosis.[6]

Table 1. Treatment options recommended by NICE for untreated CLL in adults

NICE technology appraisal guidance	Technology	Caveats of recommendation
Untreated CLL		
TA891	Ibrutinib plus venetoclax	-
TA343	Obinutuzumab with chlorambucil	Full-dose fludarabine-based therapy is unsuitable because of comorbidities and bendamustine-based therapy is not suitable
TA216	Bendamustine	Binet stage B or C disease and fludarabine combination chemotherapy is not appropriate
TA174	Rituximab with fludarabine and cyclophosphamide	Fludarabine plus cyclophosphamide is considered appropriate
For untreated CLL without a 17p deletion or TP53 mutation		
TA931	Zanubrutinib	Fludarabine plus cyclophosphamide and rituximab, or bendamustine plus rituximab is unsuitable
TA689	Acalabrutinib	
TA663	Venetoclax plus obinutuzumab	
For untreated CLL with a 17p deletion or TP53 mutation		
TA931	Zanubrutinib	-
TA689	Acalabrutinib	-
TA663	Venetoclax plus obinutuzumab	-
TA429	Ibrutinib	Chemo-immunotherapy is unsuitable
TA359	Idelalisib with rituximab	-

Table 2. Treatment options recommended by NICE for previously treated, relapsed or refractory CLL in adults

NICE technology appraisal guidance	Technology	Caveats of recommendation
Previously treated, relapsed or refractory CLL		
TA931	Zanubrutinib	Relapsed or refractory
TA689	Acalabrutinib	Previously treated
TA561	Venetoclax with rituximab	After at least 1 previous therapy
TA429	Ibrutinib	
TA359	Idelalisib with rituximab	Disease has been treated and has relapsed within 24 months
TA193	Rituximab with fludarabine and cyclophosphamide	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 CLL or in combination with chemotherapy other than fludarabine and cyclophosphamide

TA29	Fludarabine	Second-line therapy for B-cell disease when first-line chemotherapy has failed or cannot be tolerated and when the following chemotherapy regimens are options: • cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) • cyclophosphamide, doxorubicin and prednisolone (CAP) • cyclophosphamide, vincristine and prednisolone (CVP)
For previously treated CLL without a 17p deletion or TP53 mutation		
TA796	Venetoclax	After progression on both chemo-immunotherapy and a B-cell receptor pathway inhibitor
For previously treated CLL with a 17p deletion or TP53 mutation		
TA796	Venetoclax	After progression on a B-cell receptor pathway inhibitor or when a B-cell receptor pathway inhibitor is unsuitable

This evaluation will partially update TA663 and will appraise the clinical and cost effectiveness of venetoclax with obinutuzumab within its marketing authorisation for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and only when FCR or BR are suitable.

The technology

Venetoclax (Venclyxto, AbbVie) with obinutuzumab or ibrutinib is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia.

Intervention(s)	Venetoclax with obinutuzumab
Population(s)	People with untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation and for whom FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) is suitable
Comparators	• Bendamustine plus rituximab (BR) • Fludarabine with cyclophosphamide and rituximab (FCR) • Ibrutinib plus venetoclax • Acalabrutinib with venetoclax with or without obinutuzumab (subject to ongoing 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. 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** Zanubrutinib for treating chronic lymphocytic leukaemia (2023) NICE technology appraisal guidance 931. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (2023) NICE technology appraisal guidance 891. Venetoclax for treating chronic lymphocytic leukaemia (2022) NICE technology appraisal guidance 796. Acalabrutinib for treating chronic lymphocytic leukaemia (2021) NICE technology appraisal guidance 689. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2020) NICE technology appraisal 663. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (2019) NICE technology appraisal guidance TA561. 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 treatment of relapsed or refractory chronic lymphocytic leukaemia (2010) NICE technology appraisal guidance 193. 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. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (2001) NICE technology appraisal guidance 29. **Related technology appraisals in development** Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance [ID6232]. Publication date to be confirmed. **Related NICE guidelines** Haematological cancers: improving outcomes (2016) NICE guideline 47. **Related quality standards** Haematological cancers (2017). NICE quality standard 150.

References

1. NHS Choices. (2023) Chronic lymphocytic leukaemia Accessed May 2025.

2. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) incidence statistics Accessed May 2025.

3. Cancer Research UK. (2024) What is chronic lymphocytic leukaemia (CLL)? Accessed May 2025.

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. (2021) 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. BMJ Best Practice. Chronic lymphocytic leukaemia: management approach Accessed May 2025.