NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia ID6232

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of acalabrutinib and venetoclax with or without obinutuzumab within its marketing authorisation for previously 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. CLL occurs when 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. 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[1,2]. The risk of developing CLL increases with age, is more common in men, those of white ethnicity, and have a family history of CLL[2]. There were 2,936 new cases of CLL (ICD-10 code C91.1: CLL of B-cell type) in England in 2021. Of these, 1,820 were male and 1,116 were female[3].

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.

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 17p deletion or TP53 mutation[8].

Table 1. Treatment options for untreated CLL in NHS practice

NICE technology appraisal	Date	Treatment option for untreated CLL	Population
For adults with untreated CLL where mutation is not specified			
TA891	May 2023	ibrutinib with venetoclax	
TA343	June 2015	obinutuzumab with chlorambucil	for adults who have comorbidities that make full-dose fludarabine-based therapy unsuitable, and only if bendamustine-based therapy is not suitable
TA216	February 2011	bendamustine	for whom fludarabine combination chemotherapy is not appropriate
No TA published[1]		bendamustine plus rituximab	
TA174	July 2009	rituximab with fludarabine and cyclophosphamide	for whom fludarabine in combination with cyclophosphamide is considered appropriate
No TA published[8]		acalabrutinib with obinutuzumab	
Adults with untreated CLL without a 17p deletion or TP53 mutation			
TA931	November 2023	zanubrutinib	for whom fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR) is unsuitable
TA689	April 2021	acalabrutinib	If FCR or BR is unsuitable
TA663	Dec 2020	venetoclax with obinutuzumab	if FCR or BR is unsuitable
Adults with untreated CLL with a 17p deletion or TP53 mutation			
TA931	November 2023	zanubrutinib	
TA796	June 2022	venetoclax	if a B-cell receptor pathway inhibitor is unsuitable
TA689	April 2021	acalabrutinib	
TA663	December 2020	venetoclax with obintuzumab	

TA429	January 2017	ibrutinib monotherapy	for whom chemoimmunotherapy is unsuitable
TA359	October 2015	idelalisib with rituximab	

NICE Technology Appraisal Guidance 663 recommends venetoclax with obinutuzumab for use within the Cancer Drugs Fund as a treatment option for adults without a 17p deletion or TP53 mutation if FCR or BR is suitable.

The technology

Acalabrutinib (Calquence, AstraZeneca UK Ltd) as monotherapy or in combination with obinutuzumab has a marketing authorisation in the UK for treating adults with previously untreated CLL. Acalabrutinib monotherapy has a marketing authorisation in the UK for treating adults with CLL who have received at least one prior therapy.

Acalabrutinib and venetoclax with or without obinutuzumab does not currently have a marketing authorisation in the UK for untreated CLL. It is being studied in three clinical trials:

1. Acalabrutinib and venetoclax with and without obinutuzumab compared with investigators choice of chemoimmunotherapy in people with untreated CLL without the Del(17p) or TP53 Mutation[9].

2. Acalabrutinib, venetoclax and obinutuzumab compared with obinutuzumab and venetoclax in people with previously untreated high risk CLL[10].

3. Acalabrutinib and venetoclax in people with newly diagnosed CLL at high risk of infection and/or in early treatment[11].

Intervention(s)	Acalabrutinib and venetoclax with or without obinutuzumab
Population(s)	People with untreated chronic lymphocytic leukaemia
Subgroups	If evidence allows the following subgroups will be considered: • People with and without a 17p deletion or TP53 mutation • According to IgHV mutation status (mutated or unmutated)

Comparators	**For adults with untreated CLL where mutation is not specified:** • ibrutinib with venetoclax (TA891) • obinutuzumab with chlorambucil (for adults who have comorbidities that make full-dose fludarabine-based therapy unsuitable, and only if bendamustine-based therapy is not suitable) (TA343) • bendamustine (for whom fludarabine combination chemotherapy is not appropriate) (TA216) • rituximab with fludarabine and cyclophosphamide (FCR) (TA174) • bendamustine plus rituximab (BR) • acalabrutinib with obinutuzumab **For adults with untreated CLL without a 17p deletion or TP53 mutation only:** • zanubrutinib (for whom fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR) is unsuitable) (TA931) • acalabrutinib (if FCR or BR is unsuitable) (TA689) • venetoclax with obinutuzumab (if FCR or BR is unsuitable) (TA663) • venetoclax with obinutuzumab (if FCR or BR is suitable) (ID6291); subject to NICE evaluation **For adults with untreated CLL with a 17p deletion or TP53 mutation only:** • zanubrutinib (TA931) • acalabrutinib (TA689) • venetoclax with obinutuzumab (TA663) • idelalisib with rituximab (TA359) • venetoclax (if a B-cell receptor pathway inhibitor is unsuitable) (TA796) • ibrutinib (if chemo-immunotherapy is unsuitable) (TA429)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • minimal residual disease levels • event free survival • overall and complete response rate • time to treatment failure • duration of response • time to next treatment • adverse effects of treatment • infection free survival • 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 Ifor 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. Review date not stated Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (May 2023) NICE technology appraisal guidance 891. Review date not stated

	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 obinutuzumab for untreated chronic lymphocytic leukaemia (2020). NICE technology appraisal guidance 663. Review date 2023 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (2019). NICE technology appraisal guidance 561. Review date 2022 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 guidance 343. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011). NICE technology appraisal guidance 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 guidance 174. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (2007). NICE technology appraisal guidance 119. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (2001). NICE Technology appraisal guidance 29. **Related technology appraisals in development:** Pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma NICE technology appraisal guidance ID6397. Publication date to be confirmed 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. NICE technology appraisal guidance ID6291. Publication date to be confirmed

	Related NICE guidelines: Haematological cancers: improving outcomes (May 2016) NICE guideline NG47. Suspected cancer: recognition and referral (June 2015, updated October 2023) NICE guideline NG12 **Related quality standards:** Haematological cancers (2017). NICE quality standard 150.

Questions for consultation

Is it appropriate to have subgroups for those with and without a 17p deletion or TP53 mutation?

Is it appropriate to have subgroups according to IgHV mutation status (mutated or unmutated)?

Are there any other relevant subgroups?

Have all the relevant comparators for acalabrutinib and venetoclax with or without obinutuzumab been included in the scope?

Where do you consider acalabrutinib and venetoclax with or without obinutuzumab will fit into the existing care pathway for previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma?

Please select from the following, will acalabrutinib and venetoclax with or without obinutuzumab be:
A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care
D. Other (please give details):
For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.

Would acalabrutinib and venetoclax with or without obinutuzumab be a candidate for managed access?

Do you consider that the use of acalabrutinib and venetoclax with or without obinutuzumab 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 acalabrutinib and venetoclax with or without obinutuzumab 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. (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).

References

1. Chronic lymphocytic leukaemia (2023) NHS Choices. Accessed December 2024
2. What is chronic lymphocytic leukaemia (CLL)? (2024). Cancer Research UK. Accessed: December 2024
3. BMJ Best practice, Chronic lymphocytic leukaemia (2024) British Medical Journal. Accessed: December 2024
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. Cancer Registration Statistics, England 2021 (2023) NHS Digital, Accessed: December 2024.
7. 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
8. Chronic lymphocytic leukaemia: management approach (2024) BMJ Best Practice. Accessed: December 2024
9. Study of Acalabrutinib (ACP-196) in Combination With Venetoclax (ABT-199), With and Without Obinutuzumab (GA101) Versus chemoimmunotherapy for Previously Untreated CLL (AMPLIFY), (2024) Clinical Trials, Available: https://clinicaltrials.gov/study/NCT03836261, Accessed: December 2024
10. A Phase-3-trial of Acalabrutinib, Obinutuzumab & Venetoclax Compared to Obinutuzumab and Venetoclax in Previously Untreated Patients With High Risk CLL (2024), Clinical trials, Available: https://clinicaltrials.gov/study/NCT05197192, Accessed: December 2024
11. Acalabrutinib and Venetoclax Treatment of Newly Diagnosed Patients With CLL at High Risk of Infection or Early Treatment (2023) Clinical trials, Available: https://clinicaltrials.gov/study/NCT03868722, Accessed: December 2024