

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia

Final scope

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 3,157 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 unmutated immunoglobulin heavy chain gene (IgHV) may also lead to poorer 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

<i>NICE technology appraisal</i>	<i>Treatment option for untreated CLL</i>	<i>Population</i>
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

Final scope for the appraisal of ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia.

Issue Date: April 2022

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Page 1 of 5

		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
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

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 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	Ibrutinib with venetoclax
Population	People with untreated chronic lymphocytic leukaemia

Comparators	<p>For people without a 17p deletion or TP53 mutation:</p> <ul style="list-style-type: none"> • 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 <p>For people with a 17p deletion or TP53 mutation:</p> <ul style="list-style-type: none"> • acalabrutinib • venetoclax plus obinutuzumab • ibrutinib alone, for people for whom chemo-immunotherapy is unsuitable • idelalisib with rituximab.
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rates (including complete response) • minimal residual disease • adverse effects of treatment • health-related quality of life
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability and cost of biosimilar and generic products should be taken into account.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p>

<p>Other considerations</p>	<p>If the evidence allows the following subgroups will be considered:</p> <ul style="list-style-type: none"> • 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. <p>The availability and cost of biosimilar and generic products should be taken into account.</p> <p>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.</p>
<p>Related NICE recommendations</p>	<p>Related Technology Appraisals:</p> <p>Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (2021). NICE technology appraisal 689</p> <p>Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (2020). NICE technology appraisal 663.</p> <p>Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017). NICE technology appraisal guidance 429</p> <p>Idelalisib for treating chronic lymphocytic leukaemia (2015). NICE technology appraisal guidance 359</p> <p>Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015). NICE technology appraisal 343.</p> <p>Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011). NICE technology appraisal 216.</p> <p>Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal 174.</p> <p>Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (2007). NICE technology appraisal 119.</p> <p>Terminated appraisals:</p> <p>Ibrutinib with rituximab for untreated chronic lymphocytic leukaemia (terminated appraisal) (2021). NICE technology</p>

	<p>appraisal 703</p> <p>Ibrutinib with obinutuzumab for untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (terminated appraisal) (2021). NICE technology appraisal 702.</p> <p>Ofatumumab with chemotherapy for treating chronic lymphocytic leukaemia (2017) NICE technology appraisal 470 (terminated appraisal: Novartis has discontinued ofatumumab)</p> <p>Idelalisib with ofatumumab for treating chronic lymphocytic leukaemia (terminated appraisal) (2017). NICE technology appraisal 469.</p> <p>Ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal) (2017). NICE technology appraisal 452.</p> <p>Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal 344 (terminated appraisal: Novartis has discontinued ofatumumab)</p> <p>Appraisals in development (including suspended appraisals):</p> <p>Venetoclax with ibrutinib and obinutuzumab for untreated chronic lymphocytic leukaemia. NICE technology appraisals guidance ID1270. Suspended.</p> <p>Related Guidelines:</p> <p>Haematological cancers: improving outcomes (2016). NICE guideline 47 Review date to be confirmed.</p> <p>Related Quality Standards:</p> <p>Haematological cancers (2017). NICE quality standard 150.</p>
<p>Related National Policy</p>	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan</p> <p>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105.</p> <p>Department of Health (2016) NHS Outcomes Framework 2016 to 2017: Domain 1.</p>

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.

Final scope for the appraisal of ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia.

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Page 5 of 5