NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of venetoclax in combination with rituximab within its marketing authorisation for treating relapsed or refractory chronic lymphocytic leukaemia.

Background

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, weight loss and increased susceptibility to infection. People with CLL may live with a considerable burden of symptoms impacting on their quality of life whether or not they have received treatment.

CLL is a common form of leukaemia, with an estimated 3,515 new diagnoses in England each year[1]. The risk of developing CLL increases with age and is more common in men[2]. Median survival ranges from about 3 to 12 years depending on the genetic subtype and the stage at which the disease is diagnosed. Approximately 5% to 10% of people diagnosed with CLL are considered to have 'high-risk' disease. The British Committee for Standards in Haematology (BCSH) defines people with 'high risk' as those with previously untreated or relapsed CLL associated with a 17p deletion or TP53 mutation (the presence of 17p deletion or TP3 mutation influences the rate of cell growth as well as the resistance of the disease to treatment) and who require treatment, and those whose disease (regardless of biomarkers being present) relapses within 2 years of, or is refractory to purine analogue based chemotherapies (for example fludarabine)[3,4]. The BCSH defines relapse as disease progression at least 6 months after achieving a complete response or partial response. Refractory disease is defined as treatment failure or disease progression within 6 months of anti-leukaemic therapy.

Treatment options for relapsed CLL vary depending on factors such as performance status, co-morbidities and previous treatments. NICE technology appraisal guidance 487 recommends venetoclax for use within the Cancer Drugs Fund as an option for treating CLL in adults whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor. NICE technology appraisal guidance 429 recommends ibrutinib alone as an option for treating CLL in adults who have had at least 1 prior therapy. NICE technology appraisal guidance 359 recommends idelalisib in combination with rituximab for CLL in adults when the disease has been

treated but has relapsed within 24 months. NICE technology appraisal guidance 193 recommends fludarabine, cyclophosphamide and rituximab (FCR) as an option for people with relapsed or refractory CLL unless their disease is refractory to fludarabine or has been previously treated with rituximab.

The technology

Venetoclax (Venclexta, AbbVie) is an oral inhibitor of the B-cell lymphoma 2 protein that regulates cell death. Rituximab (MabThera, Roche Products) is a chimeric (mouse/human) genetically engineered monoclonal antibody. It targets the CD-20 surface marker of mature B-cell lymphocytes. It is administered by intravenous or subcutaneous infusion.

Venetoclax in combination with rituximab does not have a UK marketing authorisation for treating relapsed or refractory CLL. It is being studied in a clinical trial compared with bendamustine in combination with rituximab in adult with CLL that has progressed or relapsed after at least 1 previous therapy.

Venetoclax monotherapy has a marketing authorisation in the UK for treating CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor and for treating CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor. Rituximab has a marketing authorisation in the UK for previously untreated and relapsed or refractory CLL, in combination with chemotherapy.

Intervention(s)	Venetoclax in combination with rituximab
Population(s)	Adults with relapsed or refractory chronic lymphocytic leukaemia who have had at least 1 therapy
Comparators	• Ibrutinib • Idelalisib in combination with rituximab • Venetoclax alone • Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control, corticosteroids with or without rituximab and psychological support).

Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • 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 patient access schemes for the comparator technologies will be taken into account. The availability and cost of biosimilar products of should be taken into account
Other considerations	If the evidence allows the following subgroups will be considered: • people with a 17p deletion. 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 and NICE Pathways	**Related Technology Appraisals:** Venetoclax for chronic lymphocytic leukaemia NICE technology appraisals guidance (2017). NICE Technology Appraisal 487. Review date December 2020. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (2017). NICE Technology Appraisal 429. Review date January 2020. Idelalisib for treating chronic lymphocytic leukaemia (2015). NICE Technology Appraisal 359. Review date

	September 2018. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (2010). NICE technology appraisal guidance 202. Review deferred, awaiting results from on-going trials. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (2010). NICE Technology Appraisal 193. Guidance moved to static list. **Terminated appraisals** Ibrutinib with bendamustine and rituximab for treating relapsed or refractory chronic lymphocytic leukaemia after systemic therapy (terminated appraisal) (2017) NICE Technology Appraisal TA437. Ofatumumab in combination with chemotherapy for treating relapsed chronic lymphocytic leukaemia (terminated appraisal) (2017) NICE technology appraisal TA470. Idelalisib in combination with ofatumumab for chronic lymphocytic leukaemia (terminated appraisal) (2017) NICE technology appraisals TA469. **Appraisals in development (including suspended appraisals)** Ofatumumab for the maintenance treatment of relapsed chronic lymphocytic leukaemia [ID732]. Appraisal suspended. Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia [ID839]. Appraisal suspended. **Related Guidelines:** Improving outcomes in haematological cancer (2016). NICE guidance 47. Review date TBC. **Related Quality Standards:** Haematological cancers (2017). NICE quality standard [QS150]. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways:** Blood and bone marrow cancers (2015), NICE pathway available at: http://pathways.nice.org.uk/pathways/blood-and-bone-

	marrow-cancers
Related National Policy	Cancer Drugs Fund list (2017): https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-ver-1-55.pdf NHS England Manual for prescribed specialised services 2017/2018. Specialist cancer services (adults) [section 105, page 234]: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016). Domains 1–5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for venetoclax in combination with rituximab been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory chronic lymphocytic leukaemia after 1 prior therapy? In particular should the following be included as comparators in the scope:
  - bendamustine?
  - fludarabine plus cyclophosphamide and rituximab?
  - chlorambucil (with or without rituximab)?
  - rituximab monotherapy?
  - ofatumumab
  - venetoclax monotherapy
- How should best supportive care be defined?

Are the outcomes listed appropriate?

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

Where do you consider venetoclax in combination with rituximab will fit into the existing NICE pathway on blood and bone marrow cancers?

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 venetoclax in combination with rituximab 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.

Do you consider venetoclax in combination with rituximab 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 venetoclax in combination with rituximab can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Cancer Research UK (2014) Chronic lymphocytic leukaemia incidence statistics. Accessed December 2017.

2. Cancer Research UK (2015) Chronic lymphocytic leukaemia risks and causes. Accessed December 2017.

3. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia (2012). British Committee for Standards in Haematology. Accessed December 2017.

4. BCSH CLL guidelines interim statement 2015. Accessed December 2017.