NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ibrutinib combination therapy for untreated diffuse large B-cell lymphoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib within its marketing authorisation for treating diffuse large B-cell lymphoma.

Background

Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Lymphomas are divided into Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphomas are a diverse group of conditions which can be categorised according to their grade (how fast they grow), or the cell type affected (B-cell or T-cell), as well as by their clinical features. Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. It is a fast growing, high grade form. The symptoms differ depending on which organ or tissues are affected by the lymphoma. Non-Hodgkin lymphoma often presents as painless lumps (enlarged lymph nodes) in the neck, armpit or groin but sometimes may start in other parts of the body such as the stomach or bowel (extranodal disease). People may also have loss of appetite, tiredness or night sweats.

There are two biologically distinct subtypes of DLBCL, germinal centre B-cell (which arises in secondary lymphoid organs such as lymph node and spleen) and post-germinal centre (also known as activated B-cell lymphoma) which differ in prognosis. They are distinguished by immunohistochemical testing of gene expression profiling.

There were around 12,018 new cases of non-Hodgkin lymphoma in England in 2016 with 6,400 of these being for DLBCL.[1] Most people diagnosed with DLBCL are 65 or over.[2] Overall survival rates at 5 years for DLBCL were around 55,4% in 2004-2011.[3] However, diagnosis at early stage and post-germinal DLBCL have a better prognosis. Survival rates at 5 years were around 63.5-70.1% for stage I and II and around 51.8-46.2% for stages III and IV.[3]

Current first-line treatment is combination chemotherapy with rituximab. The most widely used first-line chemoimmunotherapy is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). Sometimes etoposide is added to this regimen or doxorubicin is substituted with a different treatment (such as gemcitabine, etoposide or liposomal doxorubicin). In addition, R-ACVBP (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone) can be used instead of R-CHOP.[4] NICE

guideline NG52 recommends central nervous system-directed prophylaxis for some people.

The technology

Ibrutinib (Imbruvica, Janssen) is an inhibitor of a protein called Bruton's tyrosine kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.

Ibrutinib with chemotherapy does not currently have marketing authorisation in the UK for treating DLBCL. It has been studied in a placebo controlled clinical trial in which ibrutinib was added to R-CHOP chemoimmunotherapy, in adults with newly diagnosed post-germinal centre DLBCL.

Ibrutinib has a marketing authorisation in the UK for treating adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or as first line treatment for patients in whom chemoimmunotherapy is unsuitable. In addition, ibrutinib has a marketing authorisation in the UK for treating adult patients with relapsed or refractory mantle cell lymphoma.

Intervention(s)	Ibrutinib with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone)
Population(s)	Adults with newly diagnosed diffuse large B-cell lymphoma
Comparators	Chemoimmunotherapy (including R-CHOP)
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 patient access schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilars should be taken into account. The use of ibrutinib is conditional on the presence of post-germinal centre B-cell lymphoma. The economic modelling should include the costs associated with diagnostic testing for the post-germinal centre subtype in people with diffuse large B-cell lymphoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • germinal centre DLBCL, and • post-germinal centre DLBCL. 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: None Related Guidelines: Non-Hodgkin's lymphoma: diagnosis and management (2016) NICE Guideline 52. Review date to be confirmed. Haematological cancers: improving outcomes (2016). NICE Guideline 47. Review date to be confirmed. Non-Hodgkin's lymphoma: rituximab subcutaneous injection (2014) NICE evidence summary of new medicines 46.

	Related Quality Standards: Haematological cancers (2017) NICE quality standard 150. Related NICE Pathways: Non-Hodgkin's lymphoma overview (2018) NICE Pathway
Related National Policy	Department of Health and Social Care (2016) NHS outcomes framework 2016 to 2017: Domains 1 and 2. NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 105, Specialist Cancer services (adults). NHS England (2017) Next steps on the five year forward view Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 NHS England (2013) NHS standard contract for cancer: Chemotherapy (Adult) Section B part 1 Service specifications. Clinical Commissioning Policy. Reference B15/S/a Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020

Questions for consultation

Have all relevant comparators for ibrutinib been included in the scope?

- What chemoimmunotherapy is used for newly diagnosed DLBCL?

Would ibrutinib be used only in combination with R-CHOP or would it be also considered in combination with other chemoimmunotherapy? If so what chemoimmunotherapy would be used?

Would ibrutinib be used for all people with newly diagnosed DLBCL or would it be considered only for people with post-germinal centre DLBCL?

- Is immunohistochemistry (IHC) and gene expression profiling (GEP) routinely used in the NHS and if so do they identify the same patients with post-germinal DLBCL?
- Are any other tests routinely used for newly diagnosed DLBCL?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom ibrutinib is expected to be more

clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ibrutinib will fit into the existing NICE pathway, Non-Hodgkin's lymphoma overview?

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 ibrutinib 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 ibrutinib 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 ibrutinib 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.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

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. Office of National Statistics (2017) Cancer Registration Statistics: England 2016 Accessed August 2018.

2. Diffuse B-cell lymphoma. Lymphoma. Accessed August 2018.

3. Cancer Research UK. Haematological Malignancy Research Network (HMRN) data (2004-2011) Non-Hodgkin lymphoma survival statistics Accessed August 2018.

4. Tilly H, Silva M, Vitolo U et al. (2015) Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* ;26(Suppl 5):v116-v125. Accessed August 2018.