NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lenalidomide with rituximab for previously treated follicular lymphoma and marginal zone lymphoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lenalidomide with rituximab within its marketing authorisation for previously treated follicular lymphoma and marginal zone lymphoma.

Background

Lymphomas are cancers of the lymphatic system, which is part of the body's immune system. They are divided into Hodgkin's and non-Hodgkin's lymphomas. Non-Hodgkin's lymphomas are a heterogeneous group of conditions ranging from 'indolent' (low-grade) to 'aggressive' (high-grade) depending on the rate at which the abnormal lymphocytes divide. Indolent lymphomas are slow growing, with long median survival times but are less likely to be cured by treatment.

Follicular lymphoma is the most common type of indolent non-Hodgkin's lymphoma. Patients with follicular lymphoma typically present with painless, swollen lymph nodes in the neck, armpit or groin. Lymphomas are commonly staged I (best prognosis) to IV (worse prognosis). The stage of the lymphoma reflects how many groups of lymph nodes are affected, where they are in the body, and whether other organs such as the bone marrow or liver are affected. Most people (80%) present with advanced disease (stage III to IV).

Marginal zone lymphoma is another type of indolent non-Hodgkin's lymphoma that develops from B lymphocytes that are normally found at the edge of areas of lymph node tissue. Mucosa associated lymphoid tissue (MALT) lymphoma is the most common type of marginal zone lymphoma and it most commonly affects the stomach. Nodal marginal zone lymphoma starts in the lymph nodes and splenic marginal zone lymphoma starts in the spleen but can also be found in the bloodstream.[1]

In 2016, approximately 12,000 people were diagnosed with non-Hodgkin's lymphoma in England, of whom around 18% had follicular lymphoma.[1,2] The 5-year survival rate is between 80 to 90% for people with follicular lymphoma and is between 50 and 80% for marginal zone lymphoma depending on the stage of disease.[3]

For untreated disease:

- NICE technology appraisal guidance 243 recommends rituximab in combination with chemotherapy as an option for untreated symptomatic stage III and IV follicular lymphoma.

- NICE technology appraisal guidance 513 recommends obinutuzumab for people who have a Follicular Lymphoma International Prognostic Index of 2 or more in combination with chemotherapy, followed by obinutuzumab maintenance therapy.

- For people who do not have symptoms, the NICE clinical guideline for non-Hodgkin lymphoma recommends that rituximab is given alone, although at the time of writing this scope rituximab monotherapy did not have a marketing authorisation in the UK for untreated non-Hodgkin lymphoma.

For treated disease:

- People whose disease does not respond to treatment, or relapses after treatment is completed, will usually receive a different combination chemotherapy regimen, with or without rituximab. Stem cell transplantation may also be considered.

- NICE technology appraisal guidance 137 recommends rituximab in combination with chemotherapy or as monotherapy for relapsed stage III or IV follicular non-Hodgkin lymphoma.

- NICE technology appraisal guidance 226 recommends rituximab maintenance therapy as an option for people whose follicular non-Hodgkin lymphoma has responded to first-line induction therapy with rituximab in combination with chemotherapy.

- NICE technology appraisal guidance 472 recommends obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance as part of the Cancer Drugs Fund for disease that is refractory to rituximab.

The technology

Lenalidomide (Revlimid, Celgene) is an immunomodulator and a structural analogue of thalidomide. It has anti-neoplastic, anti-angiogenic and pro-erythropoeitic properties. It is administered orally.

Rituximab is a genetically engineered chimeric (mouse/human) monoclonal antibody that depletes B cells by targeting cells bearing the CD20 surface marker. It is administered intravenously or subcutaneously.

Lenalidomide with rituximab does not currently have a marketing authorisation in the UK for treated follicular lymphoma or marginal zone lymphoma. It is currently being studied:

- compared with rituximab and placebo in adults with treated follicular lymphoma or marginal zone lymphoma that is not refractory to rituximab.

- compared with rituximab with chemotherapy (CHOP, CVP, or bendamustine), in adults with untreated follicular lymphoma.

- as a maintenance therapy after lenalidomide with rituximab, in adults with follicular lymphoma, marginal zone lymphoma, or mantle cell lymphoma with relapsed or refractory disease.

Intervention(s)	Lenalidomide with rituximab
Population(s)	Adults with previously treated follicular lymphoma or marginal zone lymphoma
Comparators	• Rituximab monotherapy • Rituximab in combination with chemotherapy • Established clinical management without lenalidomide (including but not limited to bendamustine)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • overall 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 technologies and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar 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 and NICE Pathways	**Related Technology Appraisals**: Idelalisib for treating follicular lymphoma that is refractory to 2 prior treatments (2014). NICE Technology Appraisal 328 (terminated). Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (2008). NICE Technology Appraisal 137. Review decision March 2011: static guidance list. **Appraisals in development (including suspended appraisals)** Idelalisib for treating refractory follicular lymphoma. NICE technology appraisal guidance [ID1379]. Publication TBC. Lenalidomide for untreated follicular lymphoma. NICE technology appraisal guidance (suspended) [ID1245]. Bortezomib for the treatment of relapsed or refractory

	follicular non-Hodgkin's lymphoma. NICE technology appraisal guidance (suspended) [ID407]. **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. **Related NICE Pathways** Non-Hodgkin's lymphoma (2016) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017, Dec 2016. Domains 1, 2, 4 and 5. NHS England, National Cancer Drugs Fund List, Aug 2018. NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapters 105 and 106 (specialist cancer services, adults and children). Department of Health and Social Care, Improving Outcomes: A strategy for cancer, fourth annual report, Dec 2014. Department of Health and Social Care, Commissioning cancer services, July 2011.

References

1 Cancer Research UK (2014) Different types of non Hodgkin lymphoma. Accessed June 2018.

2 Office for National Statistics (2018) Cancer registration statistics, England: 2016. Accessed June 2018.

3 Cancer Research UK (2004–11) Non Hodgkin lymphoma survival statistics. Accessed June 2018.