Appendix B

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisal

Idelalisib in combination with ofatumumab for chronic lymphocytic leukaemia [ID817]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of idelalisib in combination with ofatumumab within its marketing authorisation for 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, unexplained 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 2700 new diagnoses in England each year. Approximately 75% of people with CLL are diagnosed when they are over the age of 60. The risk of developing CLL increases with age and is more common in men. 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 characterised by the presence of cytogenetic mutation or abnormalities (that is, 17p deletion or TP53 mutation). The presence of 17p deletion or TP53 mutation influences the rate of cell growth as well as the resistance of the disease to treatment. People with high risk disease with the 17p deletion or TP53 mutation have a median survival of 2 to 3 years.

Treatment options vary depending on factors such as stage of CLL, performance status and co-morbidities. For people with symptomatic previously untreated CLL, NICE technology appraisal guidance 174 recommends rituximab in combination with fludarabine and cyclophosphamide (FCR) as a first-line treatment option for people who are able to take fludarabine and cyclophosphamide, but does not recommend rituximab in combination with other chemotherapies. Fludarabine monotherapy is not recommended for the first-line treatment of CLL (technology appraisal guidance TA119). Bendamustine, ofatumumab in combination with chlorambucil, and obinutuzumab in combination with chlorambucil are also are recommended as first-line treatment options in

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people for whom fludarabine combination therapy is not appropriate (technology appraisal guidance 216, 344 and 343). Chlorambucil monotherapy is also used in people for whom FCR is unsuitable. In clinical practice in England, people with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable are treated with bendamustine (with or without rituximab) or chlorambucil (with or without rituximab).

NICE technology appraisal guidance 193 recommends 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. Bendamustine is commonly used outside its marketing authorisation in clinical practice in England with or without rituximab through the Cancer Drugs Fund. Chlorambucil has a UK marketing authorisation for CLL and is used in clinical practice in England with or without rituximab in people with relapsed or refractory CLL for whom FCR is unsuitable. NICE does not recommend ofatumumab monotherapy for treating CLL refractory to fludarabine (NICE technology appraisal guidance 202).

NICE has not published guidance for ibrutinib for previously treated CLL, or idelalisib in combination with rituximab for previously treated CLL and untreated CLL that is associated with 17p deletion or TP53 mutation (NICE technology appraisals in preparation ID749 and ID764), but these treatments are used in clinical practice in England through the Cancer Drugs Fund.

The technology

Idelalisib (Zydelig, Gilead Sciences) is an oral inhibitor of serine-threonine protein kinase enzymes that regulate key cellular functions including proliferation, cell death and migration.

Idelalisib in combination with ofatumumab does not have a marketing authorisation in the UK. It has been studied in clinical trials compared with ofatumumab alone in adults with previously treated chronic lymphocytic leukaemia.

Idelalisib has a marketing authorisation in the UK in combination with rituximab for the treatment of adults with chronic lymphocytic leukaemia who have received at least one prior therapy or, as first-line treatment in the presence of 17p deletion or TP53 mutation in people unsuitable for chemo-immunotherapy.

Intervention(s)	Idelalisib in combination with ofatumumab

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Population(s)	• Adults with chronic lymphocytic leukaemia who have received at least 1 therapy • Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable

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Comparators	For adults with chronic lymphocytic leukaemia who have received at least 1 prior therapy: • Bendamustine (not licensed in the UK for this indication, funded via the CDF) with or without rituximab • Chlorambucil with or without rituximab • Fludarabine in combination with cyclophosphamide and rituximab • Ibrutinib (NICE guidance is in development, funded by the CDF in the interim) • Idelalisib in combination with rituximab (NICE guidance is in development, funded by the CDF in the interim) • Best supportive care (including but not limited to, regular monitoring, blood transfusions, infection control and psychological support) For adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation: • Bendamustine (not licensed in the UK or available through the cancer drugs fund for this indication) with or without rituximab • Chlorambucil with or without rituximab • Ofatumumab in combination with chlorambucil (recommended by NICE if the person is ineligible for fludarabine-based therapy and bendamustine is not suitable) • Obinutuzumab in combination with chlorambucil • Idelalisib in combination with rituximab (NICE guidance is in development, funded by the CDF in the interim) • Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)

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Outcomes	The outcome measures to be considered include: • overall survival • progression-free 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. Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in any economic analyses, rather than the list price. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices.
Other considerations	If the evidence allows, the following subgroup will be considered: • presence or absence of 17p deletion • presence or absence of TP53 mutation. 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	Technology Appraisal No. 344, June 2015, 'Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia'. Review Proposal Date June 2018 Technology Appraisal No. 343, June 2015, 'Obinutuzumab in combination with chlorambucil for

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	untreated chronic lymphocytic leukaemia'. Review Proposal Date June 2018 Technology Appraisal No. 202, October 2010, 'Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab'. Review Proposal Date TBC. Technology Appraisal No. 193, July 2010, 'Rituximab for the treatment of relapsed chronic lymphocytic leukaemia'. Review Proposal Date January 2014. ID764, Technology Appraisal in Preparation, 'Idelalisib for treating chronic lymphocytic leukaemia'. Earliest anticipated date of publication October 2015. ID749, Technology Appraisal in Preparation, 'Ibrutinib for treating chronic lymphocytic leukaemia'. Earliest anticipated date of publication June 2016. Related Guidelines: NICE cancer service guidance (2003). Improving outcomes in haematological cancers. Related NICE Pathways: NICE pathway on blood and bone marrow cancers, available at: http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	NHS England Manual for prescribed specialised services 2013/2014. Specialist cancer services (adults) [section 105, page 234]: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf