National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	NCRI/RCP/RCR /ACP/JCCO	There is no description of rituximab as an antibody, as opposed to a chemotherapeutic agent, and perhaps some information regarding the importance of the intracellular pathways in FL (eg NF□B) which are being targeted by such drugs as bortezomib.	The background section of the scope is intended to be a brief summary and this level of detail is not required.
	Royal College of Pathologists and British Society for Haematology	The section entitled "background" is accurate.	Comment noted.
The technology/ intervention	NCRI/RCP/RCR /ACP/JCCO	Mention of the differing toxicity profile of Bortezomib may be useful.	The scope document provides only a brief description of the technologies. The toxicity profile of bortezomib will be considered in detail as part of the appraisal process.
	Royal College of Pathologists and British Society for Haematology	To my knowledge, the description of the mechanism of action of bortezomib is accurate.	Comment noted.
Population	NCRI/RCP/RCR /ACP/JCCO	Yes. There is no particular subgroup which has been identified as having increased benefit to the technology.	Comment noted.

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	Royal College of Pathologists and British Society for Haematology	The population is not properly defined. In the UK patients with relapsed and refractory follicular lymphoma (FL) are not the same because chemotherapy is used in combination with immunotherapy. So, a patient who has refractory FL will almost have rituximab resistance. This group of patients have a very different outcome to those patients with relapsed FL who remain rituximab sensitive. It is not appropriate to group these two together. The patients with rituximab resistance, for which there is a standard definition, should be considered separately. The population should be accurately described and must address the issue of rituximab resistance. Note also that the issue of including patients who have received rituximab maintenance is not addressed- see Coiffier, lancet Oncology 2011- below)	Comment noted. The population in the draft scope has been amended to 'Adults with relapsed or refractory rituximab sensitive follicular non-Hodgkin's lymphoma' for clarification. Given that bortezomib has been studied in clinical trials in combination with rituximab, only a rituximab sensitive population will be considered for the purpose of this appraisal.
Comparators	NCRI/RCP/RCR /ACP/JCCO	bendamustine+rituximab	Comment noted. Bendamustine plus rituximab is not licensed for relapsed disease and is currently being appraised as a first line treatment. It has not been included as a comparator.

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	Royal College of Pathologists and British Society for Haematology	Chlorambucil without rituximab in relapsed FL is inappropriate and should be removed. There are two licensed therapies for rituximab resistance- bendamustine and radio-immunotherapy with Zevalin. The other therapies used in this setting and recommended in treatment algorithms are toxic therapies for aggressive lymphomas. For patients with relapsed but rituximab naieve FL, there are a range of highly effective therapies to provide a comparator- FCM-R, CHOP-R etc Rituximab monotherapy is used in Switzerland and North America but not in the UK. i.e. it is not a valid local comparator.	Comment noted. The population has been amended to state 'Adults with relapsed or refractory rituximab sensitive follicular non-Hodgkin's lymphoma'. Given that only a rituximab sensitive population will be considered for the purpose of this appraisal the comparators have been amended accordingly. Rituximab monotherapy has also been removed from the list of comparators.
Outcomes	NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Royal College of Pathologists and British Society for Haematology	Yes	Comment noted.
Economic analysis	Royal College of Pathologists and British Society for Haematology	I agree that a sufficient length of time is necessary in order to have a meaningful estimate of survival, as second and subsequent remissions can be lengthy with standard treatments.	Comment noted.
Equality and Diversity	NCRI/RCP/RCR /ACP/JCCO	None	Comment noted.

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	Royal College of Pathologists and British Society for Haematology	NA	Comment noted.
Innovation	NCRI/RCP/RCR /ACP/JCCO	Large randomised studies have shown only marginal benefit from the addition of bortezomib to standard treatment. It is a relatively costly therapy with additional toxicities. Multiple other options exist with similar benefit to that of the bortezomib-rituximab combination.	Comment noted.
Other considerations	Royal College of Pathologists and British Society for Haematology	Lancet Oncol. 2011 Aug;12(8):773-84. Epub 2011 Jul 1. Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive, follicular lymphoma: a randomised phase 3 trial.	Comment noted.
Questions for consultation	NCRI/RCP/RCR /ACP/JCCO	Given that bortezomib will be given in combination with rituximab, would it be reasonable to compare it with single agent chemotherapy without rituximab? Please define single agent chemotherapy for the purpose of this appraisal. **Only in those groups who are deemed refractory to rituximab. Chlorambucil is the most common single agent chemotherapy used in this setting.**	Comment noted. The population has been amended to state 'Adults with relapsed or refractory rituximab sensitive follicular non-Hodgkin's lymphoma'. Given that only a rituximab sensitive population will be considered for the purpose of this appraisal, the comparators have been amended accordingly.

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		Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Relapsed or refractory FL, both those who have had rituximab and those who are rituximab-naïve.**	Comment noted. The population has been amended to state 'Adults with relapsed or refractory rituximab sensitive follicular non-Hodgkin's lymphoma'.
		Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Due to the relapsing nature of the disease and the long median survival, overall survival, and QALY can be difficult to utilise as an endpoint in FL when assessing benefit. Surrogates such as Progression-free survival are often instituted in the absence of overall survival data.**	Comment noted.
		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Published phase III randomised trial data (Coiffier et al Lancet Oncol 2011, van Oers et al JCO 2010, Salles et al Lancet 2011), Published phase II data (Sehn et al , Fowler et al, JCO 2011)**	Comment noted.
	Royal College of Pathologists and British Society for Haematology	In response to the questions listed under "questions for consulatation: It is totally inappropriate to compare bortezomib + rituximab with single agent chemotherapy. Single agent chemotherapy is only relevant if the conditions of rituximab resistance have been met. In this case the only licensed chemotherapy is bendamustine. Bortezomib may prove cost-effective, compared to Zevalin and bendamustine; it may also provide for a group of patients with an unmet clinical need-rituximab resistance, effective therapy, acceptable side effects. However, there is no available data to support this in the public domain that I am aware of.	Comment noted. The population has been amended to state 'Adults with relapsed or refractory rituximab sensitive follicular non-Hodgkin's lymphoma'. Given that only a rituximab sensitive population will be considered for the purpose of this appraisal, the comparators have been amended accordingly.

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Additional comments on the draft scope.	NCRI/RCP/RCR /ACP/JCCO	Bortezomib, in combination with rituximab for relapsed follicular lymphoma, as well as in combination with chemotherapy in both the first, and second line settings has shown minimal benefit over standard therapy. Careful consideration regarding its addition to the current available options is recommended.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft scope:

Department of Health
Health care Improvement Scotland
Lymphoma Association
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing