National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Obinutuzumab for untreated advanced follicular lymphoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness		No comments	
Wording	Roche	The remit should be updated to [redacted] "To appraise the clinical and cost effectiveness of obinutuzumab within its marketing authorisation for untreated advanced follicular lymphoma".	Comment noted. The scope has been updated accordingly.
Timing Issues		No comments	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	[redacted] the description of the pathway for FL could be clarified:	Comment noted. The background section reflects the pathway

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		Rituximab in combination with chemotherapy (R-chemo) is the standard of care in induction as per the cited NICE guideline and guidance TA243. In addition to the regimens in TA243, bendamustine use in combination with rituximab in increasingly used in the first line FL setting in UK clinical practice. Bendamustine is currently funded via the Cancer Drugs Fund for indolent non-Hodgkin lymphoma, including the combination with rituximab (whereby rituximab is funded separately by baseline commissioning). In current UK clinical practice CVP, CHOP and bendamustine are now the most commonly used chemotherapy regimens used in combination with rituximab in first line FL induction treatment, accounting for over 80% of R-chemo regimens (Roche data on file 2016). For patients responding to induction, maintenance with rituximab is current standard of care in the NHS as recommended in TA226 and the NICE clinical guideline. In UK clinical practice, approximately 85% of patients receive first line maintenance in agreement with observations from the PRIMA study (Salles G et al. Lancet 2010;377:42–51, Roche data on file 2016). Although rituximab monotherapy induction treatment is now recommended in the latest NICE clinical guideline for asymptomatic advanced FL patients, this unlicensed treatment is currently not often used in clinical practice in the NHS as discussed in the appraisal of Gazyvaro for rituximab refractory FL (NICE ACD 2016 point 4.3 available at: https://www.nice.org.uk/guidance/GID-TA10020/documents/appraisal-consultation-document). These patients would currently be managed as 'watch and wait' and may then be treated with R-chemo when progressing to symptomatic disease.	described in TA243, TA226 and the NICE clinical guideline for non-Hodgkin lymphoma, and includes products available through the Cancer Drugs Fund. No action required.
The technology/ intervention	Roche	The description of the technology should be aligned with the trial design [redacted] regarding maintenance: following Cycles 6-8, in combination with chemotherapy, responding patients received Gazyvaro	Comments noted. The technology section of the scope has been updated to include more

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		maintenance therapy every 2 months until disease progression or for up to 2 years. The existing license wording should be used in the description of the rituximab-refractory FL use: "Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen."	specific information relating to the trial design and existing marketing authorisation. The exact wording of the marketing authorisation has not been used because it does not align with the NICE writing style. The intervention section of the scope does not normally include information about cycle numbers or treatment duration; the committee will appraise the technology within the boundaries of its marketing authorisation. No action required.
Population	Roche	The population should be [redacted] 'people with previously untreated advanced follicular lymphoma.'	Comment noted. The population in the scope has been updated.
Comparators	Napp	Napp agree with the inclusion of "rituximab-based chemotherapy, with or without rituximab based maintenance treatment" as a comparator for obinutuzumab. In particular for patients with previously untreated stage III-IV follicular lymphoma. We would suggest that rituximab in combination with chemotherapy followed by rituximab maintenance treatment is the most	Comments noted. Bendamustine in combination with rituximab is included in the list of comparators

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		commonly used standard of care in this setting, as outlined by NICE technology appraisals 243 and 226. [redacted] [redacted] Napp also agree with the identification of bendamustine as a potential comparator for obinutuzumab in this appraisal; although where it is used in previously untreated indolent non-Hodgkin's lymphoma (funded through the cancer drugs fund) it does not have a marketing authorisation. Based on the most recent version of the National Cancer Drugs Fund list published by NHS England, Napp would like to highlight that bendamustine may be used either as monotherapy or in combination with rituximab in what NHS England term "first line treatment of low grade lymphoma". The clinical experts involved in the appraisal should be able to outline from their experience whether bendamustine is used more frequently as monotherapy or in combination with rituximab. However Napp would suggest that use of bendamustine in combination with rituximab should be a potential comparator for NICE to consider.	(under "rituximab-based chemotherapy, with or without rituximab maintenance treatment"). The scope has been updated to reflect the potential availability of biosimilar technologies.

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		The latest iteration of the CDF list can be found here: https://www.england.nhs.uk/wp-content/uploads/2016/12/national-cdf-list-v1-14.pdf	
	Roche	The standard of care in first line treatment for advanced follicular lymphoma in NHS clinical practice is currently R-chemo induction followed by rituximab maintenance for patients responding to treatment, as described in the background information above. Therefore, rituximab-based chemotherapy with rituximab maintenance (R-chemo+R) is the appropriate comparator. Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving response (G-chemo+G) is therefore intended to replace R-chemo+R in the treatment pathway.	Comments noted. No action required.
Outcomes		No comments.	
Economic analysis	Napp	Further to the expected availability of biosimilar rituximab [redacted] Napp suggest that the scope for this appraisal be amended to consider the cost of biosimilars. Where relevant, recent NICE scoping documents have suggested “that the availability and cost of biosimilar products be taken into account”. Napp would recommend that in order to accurately reflect the true NHS acquisition cost of biosimilar medicines that tender prices are included for biosimilar medicines, not just the NHS list price. If information relating to actual tender prices is not available, Napp would suggest that uncertainty related to acquisition cost could be handled as a sensitivity analysis covering a range of discounts (e.g. 10%, 20%, 30%, 40%, 50%, etc).	Comments noted. The scope has been updated to reflect the potential availability of biosimilar technologies.

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Equality and Diversity		No equality issues were identified.	Comments noted. No action required.
Other considerations		No comments.	
Innovation	Napp	If obintuzumab is licensed for previously untreated advanced indolent non-Hodgkin's lymphoma, it will be the first anti-CD20 monoclonal antibody to be licensed for the broad indication of indolent non-Hodgkin's lymphoma – as opposed to stage III-IV follicular lymphoma like rituximab. Although rituximab may be currently used off-label for other indolent non-Hodgkin's lymphoma. For stage III-IV follicular lymphoma, where rituximab is already licensed and NICE approved, we expect the benefits of obinutuzmab may be incremental.	Comments noted. Please note that the population has been updated, as suggested by the company, to specify "untreated advanced **follicular** lymphoma". The company and other consultees will be able to fully describe why they consider obinutuzumab to be innovative in their evidence submissions, which will then be considered by the appraisal committee. No action required.
	Roche	R-chemo induction followed by maintenance with rituximab (R-chemo+R) is the standard of care for people with advanced symptomatic FL, achieving a median PFS of 6–8 years and a median survival of 12–15 years. However, FL is incurable and most people eventually relapse. Relapse occurs in 30% of patients within 3 years and is associated with a poor prognosis. Gazyvaro (G)	Comments noted. The company and other consultees will be able to fully describe why they consider

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		is a glycoengineered type II anti-CD20 monoclonal antibody with enhanced direct cell killing and antibody-dependent cellular cytotoxicity that has promising activity and manageable toxicity when combined with chemotherapy in relapsed indolent non-Hodgkin lymphoma (iNHL). The results of GALLIUM, a global, open-label, randomized Phase 3 study comparing the efficacy and safety of R-chemo+R versus G-chemo+G as first-line treatment in iNHL demonstrated a clinically meaningful improvement in PFS of G-chemo+G, with a 34% reduction in the risk of a PFS event relative to R-chemo+R therapy. Frequency of some AEs, e.g. infusion-related reactions (IRRs), cytopenias, and infections, was higher with G-chemo+G. These data support G-chemo+G becoming a new standard of care in previously untreated patients with advanced FL (Marcus AE et al. ASH 2016, https://ash.confex.com/ash/2016/webprogram/Paper94744.html)	obinutuzumab to be innovative in their evidence submissions, which will then be considered by the appraisal committee. No action required.
Questions for consultation	Roche	We consider the use of autologous stem cell transplants for people in second or subsequent remission recommended in the NICE clinical guideline as consistent with current NHS practice.	Comments noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Janssen-Cilag
Merck Sharpe & Dohme