National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma [ID841]

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness *[Would it be appropriate to refer this topic to NICE for appraisal?]*	Roche Products	Yes	Comment noted. No changes to the scope are needed.
	Royal College of Pathologists, British Society for Haematology (RCPath, BSH)	Yes. Obinutuzumab is a novel anti-CD20 antibody that will be expensive but could potentially benefit a subgroup of patients with follicular lymphoma, the commonest subtype of low grade NHL. NICE assessment is therefore important to assess cost-effectiveness.	Comment noted. No changes to the scope are needed.
Wording	Roche Products	A more appropriate wording would be: To appraise the clinical and cost effectiveness of obinutuzumab in combination with bendamustine within its marketing authorization for the treatment of patients with follicular lymphoma (FL) who are refractory to rituximab or a rituximab-containing regimen.	The wording of the remit has been amended.
	RCPath, BSH	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology?]* Partly. Rituximab is a key part of the management of follicular lymphoma and randomised trials have consistently shown survival benefits for this drug	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments	Action
		(albeit usually PFS rather than OS). Once patients have become refractory to rituximab it is therefore expected that remission durations would be substantially shorter than previously obtained. Therefore although the majority of patients with follicular lymphoma have good survival rates, this is likely to be significantly less beneficial for those who have progressed on, or shortly after, exposure to rituximab.	
Timing Issues	Roche Products	Marketing authorisation is anticipated in [redacted]	Comment noted. No changes to the scope are needed.
	RCPath, BSH	Fairly urgent as this does represent an area of unmet need.	Comment noted. No changes to the scope are needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Roche Products	The penultimate sentence should clarify that refractory is defined as; Cancers that do not respond to or progress within 6 months of treatment are termed refractory (British Committee for Standards in Haematology definition)	The definition of refractory has been added to the 'population' section of the scope.
	RCPath, BSH	See comments above - I would place more emphasis on the development of rituximab refractoriness resulting in the loss of effectiveness of an important drug in this condition, which has shown consistent survival benefits in trials.	Comment noted. The background information aims to provide a brief overview of the condition and current

Section	Consultee/ Commentator	Comments	Action
			practice. No changes to the scope are needed.
The technology/ intervention	Roche Products	The brand name should read Gazyvaro Obinutuzumab has an existing marketing authorisation in combination with chlorambucil for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) who have comorbidities making them unsuitable for full-dose fludarabine based therapy	The brand name has been amended.
	RCPath, BSH	*[Is the description of the technology accurate?]* No. It needs to be clear that the intervention is bendamustine in combination with obinutuzumab FOLLOWED BY maintenance obinutuzumab compared with single agent bendamustine. This was the trial on which this submission is based.	The description of the technology has been amended.
Population	Roche Products	Yes the population is defined appropriately.	Comment noted. No changes to the scope are needed.
	RCPath, BSH	The population needs more careful definition as 'rituximab refractory' is rather woolly. The definition should be: 'patients who have progressed on, or within 6 months of receiving, rituximab containing treatment regimens'. Within this there are 3 groups: 1. Patients who progress during induction treatment (whether it is in combination with chemotherapy or single agent rituximab). 2. Patients who progress whilst receiving a programme of rituximab maintenance treatment 3. Patients who progress within 6 months after stopping rituximab treatment	Comment noted. Attendees at the scoping workshop outlined differences between people whose disease relapses during rituximab induction therapy and those whose disease relapses during, or within 6 months of completing,

Section	Consultee/ Commentator	Comments	Action
		regimens. I think it would be appropriate to examine these different subgroups as it would NOT be common for patients in groups 1 and 2 to be treated with further rituximab; whereas in group 3 practise varies and in some institutions, patients may be rechallenged with rituximab containing regimens, especially if they are 3-6 months after the rituximab was given (as this is when levels of the antibody would be expected to be very low in the patient).	rituximab maintenance therapy. These subgroups have been added to the scope, in the 'other considerations' section.
Comparators	Roche Products	There is no definitive standard of care for these patients within England and Wales and a range of treatments as well as best supportive care are used. At the time of study design Bendamustine was the only licenced treatment for use in indolent NHL for patients who are refractory to rituximab. Subsequently Idelalisib is also licenced for use in patients who are refractory to two prior lines of treatment (note: not rituximab refractory). We are aware that clinicians will sometimes retreat patients who are refractory to a rituximab containing regimen by adding rituximab to a chemotherapy regimen. However we are unable to quantify the amount of use due to the fact that this patient population is a small sub-group of the overall usage of rituximab.	Attendees at the scoping workshop discussed the variety of chemotherapy regimens that are used in clinical practice to treat rituximab-refractory follicular lymphoma, such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil. The scope has been amended to reflect these options
	RCPath, BSH	There are 2 broad groups of patients who would have different comparators: 1. Patients considered fit for a stem cell transplant (usually < 65 year of age with few comorbidities). In many (but not all) centres, rituximab refractory	Attendees at the scoping workshop stated that it is unlikely that obinutuzumab in combination with

Section	Consultee/ Commentator	Comments	Action
		patients in this group would receive fairly intensive treatment (e.g. CHOP, ESHAP or ICE) followed by an autologous or allogeneic stem cell transplant. Bendamustine is sometimes also used to improve the remission status in these patients. A subsequent ASCT would produce a very long remission in 30-40% patients (possible cure) with low risk. An allogeneic stem cell transplant can effectively cure over 60% of patients but has higher risk: 10-20% transplant related mortality. 2. Patients not fit for stem cell transplant (usually > 65 years of age with out without comorbidities). There is no standard comparator in this group. Options include: single agent bendamustine (licensed although funding has recently become an issue as the CDF has recently withdrawn funding for this indication), idelalisib (this is licensed for patients with follicular lymphoma refractory to rituximab AND an alkylating agent - this is not not funded but is currently available through a named patient programme run by Gilead), chlorambucil, CHOP, fludarabine, fludarabine+cyclophosphamide. Rarely, patients are not fit for treatment at all. They would then receive best supportive care which may mean intermittent oral steroids and occasionally red cell transfusions.	bendamustine would be considered as an alternative to stem cell transplants. Consequently, stem cell transplants are not included as a comparator. As idelalisib is available only through a named-patient programme, it is not considered to be established practice in the NHS so is not included as a comparator. Attendees discussed the variety of chemotherapy regimens that are used in clinical practice to treat rituximab-refractory follicular lymphoma, such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil. The scope has been

Section	Consultee/ Commentator	Comments	Action
			amended to reflect these options
Outcomes	Roche Products	Rather than state overall response rate, it would be more appropriate to include response rates which can encompass overall response, complete response, partial response etc.	The outcomes have been amended to specify 'response rates'.
	RCPath, BSH	NOTE: overall survival is a very difficult endpoint in indolent lymphomas as life expectancy is long. It is highly unusual for a trial to show an OS advantage in this patient group. NICE has previously taken PFS as a suitable surrogate for OS although there is little direct evidence to support this. As early progression can be subtle and not need treatment, more relevant CLINCAL endpoints include time to next treatment, event free survival	Comment noted. Progression-free survival is included as an outcome. Time to next treatment and event free survival may be captured in the outcome 'duration of response/remission'. No changes to the scope are needed.
Economic analysis	RCPath, BSH	This is not my area of expertise	Comment noted. No changes to the scope are needed.
Equality and Diversity	RCPath, BSH	I am not aware of any issues with respect to equality	Comment noted. No changes to the scope are needed.
Innovation	Roche Products	Obinutuzumab plus bendamustine has demonstrated a doubling of PFS (15 month advantage) over bendamustine monotherapy in the pivotal trial. This is a step change in the treatment of patients who are refractory to a rituximab containing regimen.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments	Action
	RCPath, BSH	Although anti-CD20 antibodies are currently standard in the treatment of follicular lymphoma, obinutuzumab does represent a novel form of antibody (glycoengineered, type 2 with acitivity in rituximab refractory lymphoma cell lines) which could represent a significant advance for a subset of lymphoma patients. Most quality of life studies suggest that ongoing remission is associated with better quality of life scores (perhaps this is not very surprising however). Therefore lengthening remission duration may deliver a significantly improved quality of life so long as treatment related toxicities are minimal. The UK has extensive experience of rituximab use and it is recognised that immune suppression as a consequence of hypogammaglobulinaemia is seen in anti-CD20 antibody treated patients. This can sometimes lead to recurrent infections which are usually not dangerous but can be troublesome (e.g. recurrent sinusitis). It would be important to assess that obinotuzumab+bendamustine is associated with either no increased risk of infection, or a small manageable increased risk with little impairment of quality of life.	Comment noted. The outcomes have been amended to specify adverse effects of treatment including immunosuppression and infections.
Questions for consultation	Roche Products	**1** High Dose Chemo followed by stem cell transplantation could be considered an appropriate comparator for fit patients. **2** Place in pathway: Obinutuzumab in combination with bendamustine should be used in patients with follicular lymphoma who have failed one or more prior line of a rituximab containing regimen.	Attendees at the scoping workshop stated that it is unlikely that obinutuzumab in combination with bendamustine would be considered as an alternative to stem cell transplants. Consequently, stem cell transplants are not

Section	Consultee/ Commentator	Comments	Action
			included as a comparator. No changes to the scope are needed.
	RCPath, BSH	Q: Should consideration be given to subgroups based on the person's previous treatment? A: Consider looking at those whose previous treatment was rituximab monotherapy (not common practise in the UK) versus rituximab + chemotherapy (much more common practise). Q: Where do you consider obinutuzumab will fit into the existing NICE pathway, 'Blood and bone marrow cancers'? A: relapsed follicular lymphoma Q: Are there any subgroups of people in whom obinutuzumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? A: Patients who are NOT suitable for a stem cell transplant may gain more benefit as those who are fit would be expected to proceed to a transplant (in most centres but not all) and this would then be expected to produce a longer PFS irrespective of the use of obinutuzumab prior to treatment. I think all other questions are covered in the comments.	Attendees at the scoping workshop noted that induction treatment with rituximab monotherapy is uncommon in the UK, so it is not necessary to include this subgroup. Attendees at the scoping workshop stated that it is unlikely that obinutuzumab in combination with bendamustine would be considered as an alternative to stem cell transplants, in people for whom stem cell transplants are suitable. No changes to the scope are needed.
Additional comments on the	Roche Products	No	Comment noted. No changes to the scope

Section	Consultee/ Commentator	Comments	Action
draft scope			are needed.
	National Cancer Research Institute/Royal College of Physicians/ Royal College of Radiologists/ Association of Clinical Pathologists (NCRI/RCP/ RCR/ACP)	Our experts believe that the draft scope is appropriate and have no further comments to add.	Comment noted. No changes to the scope are needed.

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

Department of Health

Healthcare Improvement Scotland

Royal College of Nursing