National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab for treating relapsed or refractory classical Hodgkin 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	Bristol-Myers Squibb	We agree that use of nivolumab for the treatment of relapsed or refractory classical Hodgkin lymphoma is an appropriate and important topic for NICE appraisal.	Comment noted. No action required.
	Lymphoma Association	Although applicable to a small patient population, this is an appropriate topic for NICE guidance, given that there is no standard of care for patients in this situation and that they have limited treatment options. As such, there is a high level of unmet need.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	This is absolutely appropriate. Traditionally NICE has not always looked at this sort of area because it is rare. However this means that access to effective drugs has been problematic for rare diseases. So it is vital NICE looks at this indication.	Comment noted. No action required.
Wording	Bristol-Myers Squibb	We have no comments regarding the remit of the NICE appraisal.	Comment noted. No action required.

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	Lymphoma Association	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Our experts were unclear on what the UK licence would be, but understand that the FDA license is only for those who have relapsed after a stem cell transplant and brentuximab. However broadening it to include those who have failed 2 prior lines of treatment in whom SCT is not an option would be welcome.	Comment noted. The populations reflect the clinical trials available for nivolumab. No action required.
Timing Issues	Bristol-Myers Squibb	While we agree with the relative urgency necessary to provide timely access for cancer therapies, we feel it important to note the uncertainties inherent in providing an early submission to NICE, where clinical trial data may not be fully available. Additionally, in the specific context of relapsed or refractory Hodgkin lymphoma, where a NICE appraisal of brentuximab is ongoing, we note that the clinical pathway for Hodgkin lymphoma patients will not be standardised, leading to further uncertainties around clinical practice. However, our evidence submission will attempt to address as many of these uncertainties as possible, using scenario analyses, in order to provide a robust assessment of the cost-effectiveness of nivolumab and facilitate timely access for Hodgkin lymphoma patients.	Comment noted. NICE is aware that the early appraisal of cancer drugs may be associated with clinical uncertainties or a weaker evidence base, which the committee would take into account in its discussion. No action required.
	Lymphoma Association	Patients will be aware of nivolumab's accelerated approval by the FDA in America and that its licensing in Europe is under consideration. As such, it is right that preparation is made now through scoping for an appraisal to take place, subject to the EMA's decision.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Very urgent. Hodgkin lymphoma patients generally are young. Although relapse after ASCT and brentuximab is not common, when it happens, effective therapies are needed especially to bridge to allogeneic transplants	Comment noted. No action required.

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		which offers a potential cure.	
Additional comments on the draft remit	Bristol-Myers Squibb	None	Comment noted. No action required.
	Lymphoma Association	n/a	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol-Myers Squibb	In the absence of available NICE guidelines, treatment guidelines from the British Committee for Standards in Haematology and British Society of Blood and Marrow Transplantation form the best available evidence to inform current clinical practice for the treatment of Hodgkin lymphoma in the UK.11 It is recommended that brentuximab vedotin can be used as one of the available salvage therapies, bridging to ASCT, or can be considered amongst the alternative regimens in patients failing ASCT. Clinical experts contacted by BMS believe that patients in the UK would receive brentuximab vedotin in either setting. However, this is not currently reflected in the treatment pathway described in the draft scope. Following failure of ASCT and brentuximab vedotin, BCSH guidelines recommend that the aim of treatment in patients is to attain sufficient response to allow consideration of allogeneic transplantation in those deemed eligible and in those not deemed appropriate candidates for allogeneic transplantation, therapy should be individualised according to specific circumstance. Some patients will be most appropriately treated with a palliative approach, and early involvement of specialist palliative services is	Comment noted. The scope reflects the 2 indications for brentuximab vedotin that are relevant for this appraisal, that is, after autologous stem cell transplant, or after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option. The background section has been amended to reflect that the aim of

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		recommended. In the majority, further attempts to gain disease control are warranted, recognising that some will achieve prolonged periods of disease control. As such, we agree that there is no standard therapy administered in this patient population.	treatment is to allow allogeneic stem cell transplant in people in whom this procedure is suitable.
	Lymphoma Association	In the first paragraph, the text indicates the swelling of lymph nodes as the initial symptom of Hodgkin's lymphoma. While this is often the case, swelling is not always present as a symptom, which explains why diagnosis can sometimes be delayed. In the later paragraphs, there is no reflection of the fact that brentuximab vedotin is also used as a bridge to transplant for some patients (given that the treatment is currently available on the NHS via the CDF).	Comment noted. The scope has been amended to reflect that the swelling of lymph nodes occurs often rather than always. The scope reflects the 2 indications for brentuximab vedotin that are relevant for this appraisal, that is, after autologous stem cell transplant, or after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option.
	NCRI-ACP-RCP-RCR	The World Health Organisation have stated it should be 'Hodgkin' not 'Hodgkin's' lymphoma. Nodular LP Hodgkin is not characterised by Reed-sternberg cells at all. It is	Comment noted. The disease is now referred to as 'Hodgkin lymphoma' throughout

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		odd to say they are contain ‘very few’. Brentuximab is also now licensed for consolidation following ASCT for patient with high risk relapsed classical Hodgkin Lymphoma Our experts would not regard ChlVPP as in any way a standard after ASCT and BV. It is very myelotoxic and would cause a lot of difficulties used at this stage of treatment. Gemcitabine yes. Also bendamustine (although it is not formally funded in the UK, some trusts do give it with good effect)	the scope. The scope has been amended to state that the nodular lymphocyte predominant type does not contain Reed-Sternberg cells. The indication of brentuximab vedotin for consolidation therapy is not considered relevant to this appraisal. ChlVPP has been excluded as a possible comparator for nivolumab in the scope.
The technology/ intervention	Bristol-Myers Squibb	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
Population	Bristol-Myers Squibb	No comment	No action required.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.

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Comparators	Bristol-Myers Squibb	As stated above, following failure of ASCT and brentuximab vedotin, BCSH guidelines recommend that the aim of treatment in patients is to attain sufficient response to allow consideration of allogeneic transplantation in those deemed eligible and in those not deemed appropriate candidates for allogeneic transplantation, therapy should be individualised according to specific circumstance. Some patients will be most appropriately treated with a palliative approach, and early involvement of specialist palliative services is recommended. In the majority, further attempts to gain disease control are warranted, recognising that some will achieve prolonged periods of disease control. As such, we agree with the background of the scope that there is no standard therapy administered in this patient population, and so we suggest that there is no established clinical management.	Comment noted. For people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin, the comparators in the scope have been amended to include established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine, and best supportive care.
	NCRI-ACP-RCP-RCR	As mentioned above, we would NOT regard ChlVPP as a standard post ASCT and BV. In fact there really are no standards. Apart from nivolumab and pembrolizumab there is very little published data at all for the use of drugs in this situation. Generally options are: clinical trial (often the first choice in this group if available), gemcitabine, bendamustine (not routinely available but is used to good effect by some trusts). For people in whom SCT is not an option, and failed 2 lines. BV is now standard. Followed by BSC. BSC is occasional steroid treatment to help with itch and night sweats, blood transfusions as needed and possibly palliative	Comment noted. For people with relapsed or refractory classical Hodgkin lymphoma following autologous stem cell transplant and brentuximab vedotin, the comparators in the scope have been

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		radiotherapy to areas of pain.	amended to include established clinical management without nivolumab including chemotherapy such as gemcitabine or bendamustine, and best supportive care.
Outcomes	Bristol-Myers Squibb	We suggest inclusion of partial response rate and rate of stable disease as outcome measures of interest. Clinical experts contacted by BMS consider achievement of these outcomes to be clinically significant in this patient population when receiving nivolumab treatment. As such, these outcomes should be considered within the scope of this assessment.	Comment note. The outcomes have been amended to include 'response rates', which would encompass the measures of anti-tumour effect such as partial response rate and rate of stable disease.
	NCRI-ACP-RCP-RCR	Our experts would also include duration of remission. Otherwise we agree although the trials involving nivolumab are very recent so overall survival is not particularly relevant yet.	Comment noted. The scope is not intended to provide an exhaustive list of the all the outcomes of potential relevance. Duration of remission was not considered a

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			key outcome that would be included in the economic model.
Economic analysis	Bristol-Myers Squibb	No comments	No action required.
	NCRI-ACP-RCP-RCR	The trials of nivolumab have short follow up so we are not sure how NICE will do this.	Comment noted. The data observed during the follow-up period of the trial are normally 'extrapolated' over a lifetime time horizon to estimate the lifelong costs and benefits of treatment. No action required.
Equality and Diversity	Bristol-Myers Squibb	No comments	No action required.
	NCRI-ACP-RCP-RCR	The only issue is that IF the remit ends up only being relapse post ASCT and BV, this will discriminate against older and comorbid patients in whom ASCT is not an option. Another reason why our experts would support this being considered.	Comment noted. Nivolumab will be appraised by NICE for all the populations included in its marketing authorisation. No action required.

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Innovation	Bristol-Myers Squibb	BMS consider nivolumab to be innovative in the treatment of Hodgkin lymphoma, due to its novel mechanism of action in this therapeutic area and the potential for it to make a significant impact on the substantial unmet need. Nivolumab is a novel immunotherapy agent for the treatment of cancer, with a new mechanism of action as a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. It specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the binding of the PD-L1 and PD-L2 ligands found at the tumour site to PD-1 receptors on immune cells. This approach, enabling the body's own immune system to target cancer, is novel in Hodgkin lymphoma and is viewed by physicians and patient interest groups as a 'step-change' in the management of relapsed or refractory Hodgkin lymphoma. In patients with relapsed or refractory Hodgkin lymphoma following ASCT and brentuximab vedotin, outcomes are poor, with short survival and no recommended treatment options, so that there is significant unmet need in this patient population. Similarly, there are even fewer treatment options in patients who are not eligible for ASCT due to chemorefractory disease, advanced age or co-morbidities. Based on available data relating to nivolumab, this is of major interest for public health, in particular from the view point of therapeutic innovation, as it has the potential to offer an alternative therapeutic option with an expected improved significant benefit over management of patients in the absence of nivolumab.	Comment noted. The company is encouraged to describe the innovative nature of nivolumab in its submission to NICE. No action required.
	Lymphoma Association	Yes, as a novel immunotherapy agent, nivolumab is innovative, with a new mode of action and represents a step change in the management of relapsed/refractory Hodgkin lymphoma for this group of patients.	Comment noted. The innovative nature of nivolumab will be taken into account in the

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			committee's discussion. No action required.
	NCRI-ACP-RCP-RCR	This is a hugely innovative technology. Hodgkin is an extremely immunologically 'hot' tumour in which Reed-Sternberg cells express abundant PD1 ligand so it is an ideal tumour in which to use PD1 inhibitors. In fact the activity of nivo in Hodgkin is FAR greater than activity seen in other licensed indications such as melanoma.	Comment noted. The innovative nature of nivolumab will be taken into account in the committee's discussion. No action required.
Other considerations	Bristol-Myers Squibb	No comment	No action required.
	Lymphoma Association	From conference presentations it is clear that the clinical trial data is not fully complete, so patients and patient groups would hope that there is flexibility and understanding in NICE's evaluation and assessment methodology to allow and provide for any uncertainties that may result.	Comment noted. NICE is aware that the early appraisal of cancer drugs may be associated with clinical uncertainties or a weaker evidence base, which the committee would take into account in its discussion. No action required.
	NCRI-ACP-RCP-RCR	Note that in the UK we often use drugs in this setting as a bridge to allogeneic SCT. This is somewhat different to the practise abroad. So the average number of infusions is likely to be less in the UK than in other countries	Comment noted. The company would be expected to address the

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		potentially making it more cost effective.	uncertainty about the number of infusions received in its submission to NICE. No action required.
Questions for consultation	Bristol-Myers Squibb	None	No action required.
	NCRI-ACP-RCP-RCR	The comparator issue has already been addressed. Allogeneic transplant should NOT be considered a comparator as the drug would often be used as a bridge TO transplant, not instead of transplant. BSC: occasional courses of steroid, blood product support, palliative radiotherapy to areas of pain, pharmacological interventions to help itch and pain. Outcomes: yes, but data too immature for OS to be meaningful and I would also include duration of remission	Comment noted. No action required.
Additional comments on the draft scope	Bristol-Myers Squibb	None	No action required.
	NCRI-ACP-RCP-RCR	We applaud NICE for looking at this. Hodgkin is the commonest cancer in the teenage young adult population and multiply relapsed disease has a huge impact on the patient, families and society even though it's rare.	Comment noted. No action required.

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

The Department of Health