National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

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

Comment: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Bristol-Myers Squibb BMS (BMS)	The remit in the draft scope does not reflect the proposed indication submitted to the regulatory authorities. BMS suggest: To appraise the clinical and cost-effectiveness of nivolumab within its anticipated marketing authorization [redacted] In accordance to the above the remit of the draft scope should be updated to reflect the proposed marketing authorisation.	Comment noted. The remit may be broader than the proposed marketing authorisation. However, NICE can only issue guidance within the marketing authorisation of a technology.
	The British Association of Skin Cancer Specialist Nurses (BASCSN)	The wording is accurate for the purpose of this appraisal	Comment noted.

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Timing Issues	BMS	Nivolumab is anticipated to become the first immuno-oncology agent to receive EMA approval [redacted] It is important for NICE to provide a recommendation for the use of nivolumab within the NHS as close to marketing authorisation as possible, given the high unmet medical need and the lack of effective and tolerable adjuvant treatment options for resected stage III or IV melanoma. Currently, the EMA approved therapies for treatment of resected melanoma in the adjuvant setting include interferon alfa-2b.[1, 2] However, adjuvant therapy is not common clinical practice in the UK. Therefore, following resection most patients are simply monitored through routine surveillance and receive no active treatment.[3] As a result, relapse rates are high with recurrent disease reported in up to 89% of patients (stage dependent 5 year relapse rate) which is associated with extremely poor 5 year survival rates from 11% to 20% (stage dependent) [4]	Comment noted. NICE may only make a recommendation within the marketing authorisation of a technology.
	BASCSN	Urgent. There are currently no effective adjuvant treatments for melanoma at this earlier stage. The sooner this treatment is available in an adjuvant setting, the better for NHS patients diagnosed with Stage III/IV resected disease	Comment noted.

Comment: the draft scope

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Background information	BMS	The background section should be expanded to include estimates of melanoma patients which go on to experience relapse following complete resection. Despite the surgery, melanoma patients with stage III and Stage IV disease patients undergoing complete resection are at high risk for relapse and death. In a SLR of mainly northern European studies, 5-year relapse-free survival was 28-44% for Stage III melanoma patients.[5] Following relapse, patients may go on to develop advanced or metastatic disease. As noted in the draft scope, adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in clinical practice. The aim of adjuvant treatment following complete resection of stage III or IV melanoma is to prevent disease recurrence which is associated with worse survival outcomes, reduced health related quality of life and increased healthcare costs. An effective adjuvant treatment would therefore be of great benefit to patients and healthcare services alike.	Comment noted. The scope has been amended to incorporate this information in the background section.
	BASCSN	The background information is accurate and pertinent to the appraisal	Comment noted.
The technology/ intervention	BMS	BMS suggest adding more information regarding the primary clinical study informing this submission. The efficacy and safety of nivolumab for the treatment of adjuvant melanoma after complete resection of stage III/IV Melanoma is investigated in the CheckMate 238 study. CheckMate 238 is an ongoing Phase III study of adjuvant therapy with Nivolumab versus Ipilimumab after complete resection of Stage III/IV Melanoma. Participants were randomised 1:1 to receive maximum of 1 year treatment with nivolumab or ipilimumab. For further	Comment noted. This section of the scope is intended as a brief overview of the clinical evidence which would support a submission. No further detail is required at this stage

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		details regarding the study design, inclusion criteria and detailed results please refer to the study article by Weber J et al 2017.[6]	and the scope has not been amended.
	BASCSN	The technology description for Nivolumab in terms of melanoma use is accurate.	Comment noted.
Population	BMS	BMS does not believe that the proposed population for this appraisal is reflective of the anticipated MA indication: [redacted] The population for this technology appraisal should be updated to reflect that of the regulatory application submitted to the EMA. [redacted]	Comment noted. Given the commercial in confidence nature of the proposed indication, the population has been informed by the clinical trial. However, NICE will only issue guidance within the marketing authorisation of a technology.
	BASCSN	Population correctly defined in this proposed use of Nivolumab	Comment noted.
Comparators	BMS	BMS agree with the draft scope that the most relevant comparator for the UK is routine surveillance. UK clinicians have validated this to be the most relevant comparator for this patient population. Routine surveillance is defined in the current practice within the NICE treatment pathways for stage III melanoma. Currently it is recommended that routine surveillance with computerized tomography (CT) for this population is offered every 3 months for the first 3 years after completion of treatment, then	Comment noted.

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		every 6 months for the next 2 years. Patients are subsequently discharged at the end of 5 years. For these patients surveillance imaging may also be offered as part of follow-up on a 6 monthly basis (NICE NG14[3]). For patients with Stage IV resected disease NICE NG14 recommends personalised follow up.	
	BASCSN	Routine surveillance is the standard comparator	Comment noted.
Outcomes	BMS	BMS do not believe the inclusion of "Duration of response" is a relevant outcome for this technology appraisal. This endpoint is not relevant for an adjuvant trial setting and was therefore not included in CA209-238 study design. Therefore, should be removed from the final scope.	Comment noted. Duration of response has been removed as an outcome in the scope.
		Correct outcome measures to capture the most important health related benefits of proposed treatment with Nivolumab	Comment noted.
Economic analysis	BMS	BMS have no further comments in regards to the proposed economic analysis.	Comment noted.
	BASCSN	No changes required. Appropriate patient group identified.	Comment noted.
Equality and Diversity	BMS	The proposed analysis is appropriate	Comment noted.
	BASCSN	No changes required. Appropriate patient group identified.	Comment noted.
Innovation	BMS	BMS consider nivolumab to be an innovative technology [redacted]	Comment noted.

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		[redacted] Nivolumab will be the first immunotherapy agent to receive a MA for the above indication from the EMA. 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 and is viewed by physicians and patient groups as a 'step-change' in its management. Patients with resected stage III or IV melanoma have an increased risk of recurrent disease which is associated with treatment challenges and poor survival outcomes of advanced and metastatic disease and increased health care costs.[7] Nivolumab acts primarily within the tumour microenvironment, while adjuvant therapy targets micrometastatic disease which is the source of future mortality from melanoma recurrence, therefore reducing the risk of relapse in this population.[8] In the CheckMate 238 clinical study, nivolumab administered as adjuvant treatment was associated with statistically significant improvements in recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) compared to ipilimumab[6], which has previously demonstrated statistically significant improvements in RFS and overall survival (OS) against placebo, representative of routine surveillance.[9] Such prevention of disease recurrence is associated with survival benefits, quality of life benefits and reduced healthcare costs.	

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		Due to its novel mechanism of action nivolumab can make a significant impact this patient population by preventing disease relapse following complete resection of stage III or IV melanoma. In particular from the view point of therapeutic innovation, nivolumab has the potential to offer an active treatment option for patients in the adjuvant setting with significant benefit over the current routine surveillance standard of care available in the UK by reducing relapse and thus need for long-term systemic treatment in the post-adjuvant (often metastatic) setting.	
	BASCSN	The benefit to patients in the use of Nivolumab for stage IV unresected disease has already been established. As there is currently no effective adjuvant treatment for melanoma at the resected stage III/IV point on the clinical pathway for malignant melanoma, the use of Nivolumab in this setting is likely to provide an innovative opportunity to improve overall survival for this patient group Checkmate 238 study Adjuvant Nivolomab versus Ipilumimab in resected stage III or IV melanoma Weber et al NEJM Sept 2017	Comment noted.
Other considerations	BMS	None.	Comment noted.
	BASCSN	None	Comment noted.

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Questions for consultation	BMS	Are there any adjuvant treatments considered to be established clinical practice in the NHS for adjuvant treatment following complete resection of stage III or stage IV melanoma? NICE have not conducted a HTA on the EMA approved adjuvant treatments following surgical resection of Stage III or IV melanoma. To date, due to the high toxicities associated with these treatments their uptake and use in the UK has been very limited. UK clinicians confirm that the current standard of care follows the NICE pathway outlined in NG14 and constitutes of routine surveillance for a maximum of 5 years post resection. No drugs are listed in the CDF for adjuvant treatment of resected melanoma. This suggests that patients would not have access to any treatments in the adjuvant setting following resection of stage III or IV melanoma unless recruited in clinical study.[10] **Are the outcomes listed appropriate?** No. BMS suggest removal of “Duration of response” from the final scope as is not a relevant outcome for an adjuvant setting trial setting and was therefore not included in CA209-238 study design. **Are there any subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?**	Comments noted. The response to consultation comments have been responded to above.

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		No. BMS do not believe there exist currently any subgroups which should be examined separately. **Where do you consider nivolumab will fit into the existing NICE pathway for Melanoma?** Patients with sential lymph node micro-metastases of stage III melanoma currently receive surgery for complete lymphadenectomy or therapeutic lymph node dissection when with palpable stage IIIB or IIIC melanoma or nodal disease detected by imaging. Subsequent to this, patients are routinely monitored every 3 months for the first 3 years and every 6 months for the next 2 years with patients being discharged at the end of the 5 years. Surveillance imaging can also be offered to Stage III melanoma patients. For patients with Stage IV melanoma, following referral to specialist skin cancer multidisciplinary teams for staging and management, melanoma surgery or other ablative treatments may be considered to prevent and control oligometastatic disease. Intralesional treatment can include talimogene laherparepvec, while treatments for advanced or metastatic melanoma available in the NHS include immunotherapy (ipilumumab[11], nivolumab[12], nivolumab with ipilimumab combination[13], pembrolizumab[14, 15]) and targeted therapies for BRAF V600 positive melanoma (dabrafenib[16], vemurafenib[17], trametinib in combination with dabrafenib[18]). **Do you consider nivolumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**	

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		BMS consider nivolumab to be an innovative treatment option in the adjuvant melanoma setting [redacted] Nivolumab will be the first immunotherapy agent to receive a MA for the above indication from the EMA, and will therefore be the first active treatment option available in for patients which are currently managed through routine surveillance. In the CheckMate 238 clinical study, nivolumab administered as adjuvant treatment was associated with statistically significant improvements in recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) compared to ipilimumab[6], which has previously demonstrated statistically significant improvements in RFS and overall survival (OS) against placebo, representative of routine surveillance.[9] Due to its novel mechanism of action, nivolumab has the potential to make a significant impact in this patient population by preventing disease recurrence following complete resection, therefore improving overall survival and quality of life and reducing healthcare costs associated with the treatment of advanced/metastatic disease. **Do you consider that the use of nivolumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** BMS believe that the QALY adequately captures all of the patient-orientated health benefits relevant for the HTA. However, the curative potential	

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		associated with immunotherapy such as nivolumab, and the possible return to normal living that this offers patients is a remarkable advance from what is currently achieved in the adjuvant setting. Furthermore, as melanoma disproportionately affects a younger population, this has a significant impact on the working age population, mainly a loss of economic productivity, which is not captured in the QALY calculation. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** The HTA will make use of the Checkmate 238 study (nivolumab versus ipilimumab) and Checkmate 029 (ipilumumab versus placebo) to inform the HTA submission. The lack of overall survival data from Checkmate 238 may require the application of further analytical or modelling methods to inform the economic model. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No.	
	BASCSN	No other effective treatments currently available for melanoma at this defined stage of the disease. The outcomes are listed appropriately The main group to benefit from this appraisal has been clearly identified.	Comments noted.

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		Nivolumab as a treatment for metastatic melanoma has made a significant difference in survival for metastatic patients, this treatment is likely to reduce the risk of patients developing metastatic disease. Nivolumab as an adjuvant agent will fit in well to the exisiting clinical pathway for this disease, providing patient opportunity where none existed previously at this stage. This will provide a 'step-change' in the management of malignant melanoma. This treatment is generally well tolerated with the majority of patients being able to carry out all activities of daily living including going to work. While there are possible adverse effects from this treatment, these are now well identified and can be managed effectively. Overall there are likely to be significant health benefits to those individuals affected by this disease. This treatment will inevitably have an impact on resources and capacity. This will hopefully be mitigated in the future with a reduction in the number of patients needing treatment for metastatic disease. I cannot foresee any barriers in the adoption of this potential treatment into mainstream practice.	
Additional comments on the	BMS	None	Comment noted.

Section	Consultee/ Commentator	Comments	Action
draft scope			

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

Department of Health