National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously treated with ipilimumab

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	British Association of Dermatologists	Yes	Comment noted.
	Merck Sharp & Dohme	MSD agrees that it is appropriate for this topic to be referred to NICE for appraisal. Please note that the title of this proposed appraisal requires correction. We request this be changed to 'Pembrolizumab for treating advanced melanoma in people who have been previously treated with ipilimumab'.	Comment noted. The title for this proposed appraisal has been updated to 'Pembrolizumab for treating advanced melanoma previously treated with ipilimumab'.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
Wording	British Association of	Yes	Comment noted.

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	Dermatologists		
	Merck Sharp & Dohme	Please note that the indication referred to in the draft scope is no longer consistent with the proposed indication in the regulatory submission currently under review. The proposed licence indication will be treatment of unresectable or metastatic melanoma in adults. However it is intended that we will make two separate submissions to NICE, covering the following populations separately: • People who have been previously treated with ipilimumab [ID760] • People previously untreated with ipilimumab [ID801]	Comment noted. It was agreed at the scoping workshop that the draft remit for this appraisal should be updated to 'To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating advanced melanoma'. The appraisal of pembrolizumab for treating advanced melanoma previously untreated with ipilimumab will be considered separately.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
Timing Issues	Merck Sharp & Dohme	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval.	Comment noted. NICE aims to schedule technology appraisals

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			into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to issue guidance within 6 months of a technology receiving its marketing authorisation in the UK. NICE will consider this appraisal under its single technology appraisal process.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Outcomes from advanced melanoma remain poor, with average life expectancy under 12 months for the majority. So new, effective treatments are urgently needed	Comment noted. NICE aims to schedule technology appraisals into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to issue guidance within 6 months of a technology receiving its marketing authorisation in the UK. NICE will consider this appraisal under its single technology appraisal process.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Merck Sharp & Dohme	Currently the background section does not reflect TA319: ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma, published July 2014. Following positive NICE guidance, Ipilimumab will now be routinely available as first line treatment.	Comment noted. The background section in the scope has been updated accordingly.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	First line therapy for advanced melanoma is now rarely dacarbazine. The majority of patients with a BRAF mutation will receive a BRAF inhibitor. Following the most recent NICE guidance TA319, ipilimumab will be offered as first line therapy for the majority of BRAF WT patients as well as in some BRAF mutant melanoma patients with low volume, slowly progressing disease	Comment noted. The background section in the scope has been updated accordingly.
The technology/ intervention	British Association of Dermatologists	Yes	Comment noted.
	Merck Sharp & Dohme	The word 'refractory' may be ambiguous and open to interpretation. Therefore we suggest it would be preferable to replace 'people whose disease is refractory to ipilimumab' with 'people previously treated with ipilimumab'	Comment noted. It was agreed at the scoping workshop that the term 'refractory' should be removed and the population updated to 'People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with

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			ipilimumab.'
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
Population	British Association of Dermatologists	No subgroups have yet been identified to our knowledge.	Comment noted. No subgroups have been specified in the scope.
	Merck Sharp & Dohme	We suggest the following correction and re-wording: "People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab".	Comment noted. It was agreed at the scoping workshop that the term 'refractory' should be removed and the population updated to 'People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab.'
Comparators	British Association of Dermatologists	Should nivolumab be included?	Comment noted. It was agreed at the scoping workshop that nivolumab should not be included as a

Section	Consultee/ Commentator	Comments	Action
			comparator in the scope because it is not established clinical practice in the NHS at the moment.
	Merck Sharp & Dohme	MSD does not agree with the proposal to include dacarbazine as a comparator in this appraisal. This appraisal will be focused on the population of patients who have experienced disease progression after previous therapy with ipilimumab. For such patients, we cannot envisage a scenario where patients would subsequently receive dacarbazine as a stand-alone new therapy option after ipilimumab therapy. Consequently, dacarbazine would be an inappropriate comparator in this appraisal. MSD does not agree with the proposal to include temozolomide as a comparator in this appraisal. Temozolomide was not included as a comparator in either the previous ipilimumab or vemurafenib NICE appraisals. Please note that Temodal (temozolomide) is manufactured by MSD and is not indicated for the treatment of advanced melanoma. MSD supports the proposal to include best supportive care as a comparator. Additionally, we suggest it is important to also include vemurafenib as a comparator in this setting. In clinical practice, we understand that clinicians sometimes choose to treat BRAF mutation-positive, low tumour burden patients using ipilimumab as first line therapy, saving vemurafenib with its faster onset of action as salvage therapy. In such a scenario, vemurafenib would be a potential comparator to pembrolizumab.	Comment noted. It was agreed at the scoping workshop that dacarbazine is still used for some patients in clinical practice in the NHS and therefore should be included in the scope. Following the scoping workshop, the comparators in the scope have been updated: temozolomide (for people with brain metastases) has been removed and vemurafenib (for people with BRAF V600 mutation-positive disease) and dabrafenib (for people with BRAF V600 mutation-positive disease) have been

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			added to the scope.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	The standard comparators should include vemurafenib for those BRAF mutant melanoma patients who received ipilimumab as first line therapy. Temozolamide is not routinely offered to brain mets patients in the UK	Comment noted. Following the scoping workshop, the comparators in the scope have been updated: temozolomide (for people with brain metastases) has been removed and vemurafenib (for people with BRAF V600 mutation-positive disease) and dabrafenib (for people with BRAF V600 mutation-positive disease) have been added to the scope.
Outcomes	British Association of Dermatologists	Yes	Comment noted.
	Merck Sharp & Dohme	Agree	Comment noted.
	RCP on behalf of NCRI/RCP/RCR	Yes	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	/ACP/JCCO		
Economic analysis	Merck Sharp & Dohme	No additional comments	Comment noted.
Equality and Diversity	British Association of Dermatologists	We are not aware of any discriminating factors.	Comment noted. No equality issues have been raised during consultation or at the scoping workshop.
	Merck Sharp & Dohme	No additional comments	Comment noted. No equality issues have been raised during consultation or at the scoping workshop.
Innovation	British Association of Dermatologists	Yes	Comment noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process.
	Merck Sharp & Dohme	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits.	Comment noted. Consultees are

Section	Consultee/ Commentator	Comments	Action
			encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	This first anti PD-1 McAb is a step change in the management of metastatic melanoma	Comment noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process.
Other considerations	Merck Sharp & Dohme	No additional comments	Comment noted.
NICE Pathways	British Association of Dermatologists	Where do you consider pembrolizumab will fit into the existing NICE pathway Skin cancer overview: melanoma? Therapeutic option for advanced stage 3 and 4 melanoma.	Comment noted.
	Merck Sharp & Dohme	Question: Where do you consider pembrolizumab will fit into the existing NICE pathway Skin cancer overview: melanoma? Answer: We consider that pembrolizumab should be offered as an alternative	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		option for treating advanced (unresectable or metastatic) melanoma in people who have been previously treated with ipilimumab [proposed STA ID760] , and in people previously untreated with ipilimumab [proposed STA ID801]. With regards to the proposed appraisal in the population of patients previously treated with ipilimumab [ID760], we envisage pembrolizumab being used as second and third line treatment options as per the following sequences: • ipilimumab; pembrolizumab • ipilimumab; vemurafenib; pembrolizumab • vemurafenib; ipilimumab; pembrolizumab	
Questions for consultation	British Association of Dermatologists	How is disease refractory to ipilimumab defined in clinical practice? Evidence of disease progression.	Comment noted. It was agreed at the scoping workshop that the term 'refractory' should be removed and the population updated to 'People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab.'
	Merck Sharp & Dohme	Question: Which treatments are considered to be established clinical practice in the NHS for advanced melanoma in people whose disease is refractory to ipilimumab? Response: BSC	Comment noted. It was agreed at the scoping workshop that the term 'refractory'

Section	Consultee/ Commentator	Comments	Action
		Question: How should best supportive care be defined? Response: MSD suggests best supportive care should be defined as no active treatment (palliative care only) Question: How is disease refractory to ipilimumab defined in clinical practice? Answer: MSD suggests all references to 'refractory to ipilimumab' should be rephrased as 'previously treated with ipilimumab' to avoid ambiguity or potential for confusion.	should be removed and the population updated to 'People with advanced (unresectable stage III or stage IV) melanoma whose disease has progressed after previous treatment with ipilimumab.'

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 Pathologists

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)	British Association of Dermatologists		Included	This organisation has an area of interest related to this appraisal topic and meets the selection criteria to participate in this appraisal. (BAPRAS) has been added to the matrix of consultees and commentators under 'professional groups'.

2.	Bayer (dacarbazine)	NICE Secretariat		Added	This organisation is a comparator for this appraisal topic. Bayer has been added to the matrix of consultees and commentators under 'comparator companies'.
3.	Glaxo Smith Kline (dacarbazine)	NICE Secretariat		Added	This organisation is a comparator for this appraisal topic. Glaxo Smith Kline has been added to the matrix of consultees and commentators under 'comparator companies'.
4.	Roche (vemurafenib)	NICE Secretariat		Added	This organisation is comparator for this appraisal topic. Roche has been added to the matrix of consultees and commentators under 'comparator companies'.

5.	Health Research Authority	NICE Secretariat	Removed	Removed	This organisation no longer wishes to be added to appraisal topic. Health Research Authority has been removed from the matrix of consultee and commentator under 'relevant research groups'
6.	Merck Shape and Dohme (temozolomide)	NICE Secretariat		Removed	This organisation is not a comparator for the appraisal topic. Merck Sharpe and Dohme has been removed from the matrix of consultees and commentators under 'comparator companies'.
7.	Teva (temozolomide)	NICE Secretariat		Removed	This organisation is not a comparator for the appraisal topic. Teva has been removed from the matrix of consultees and commentators under 'comparator companies'

8.	Zentiva UK (temozolomide**)**	NICE Secretariat		Removed	This organisation is not a comparator for the appraisal. Zentiva has been removed from the matrix of consultees and commentators under 'comparator companies'