National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated 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.
	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	MSD agrees that it is appropriate for this topic to be referred to NICE for appraisal.	Comment noted.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Roche Products	No comment	Comment noted.
Wording	British Association of	Yes	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Dermatologists		
	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	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 previously untreated with ipilimumab [ID801] •People who have been previously treated with ipilimumab [ID760]	Comment noted. It was agreed at the scoping workshop that the draft remit for this was appropriate. The appraisal of pembrolizumab for treating advanced melanoma previously treated with ipilimumab will be considered separately.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Roche Products	No comments	Comment noted.
Timing Issues	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	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 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	Ipilimumab offers a durable response in only around 20% of those patients treated, so better treatments (with fewer side effects) likely to improve outcomes in more patients 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

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			appraisal under its single technology appraisal process.
	Roche Products	No comments	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Bristol-Myers Squibb Pharmaceuticals	In the last paragraph it reads "First-line treatment normally involves the administration of dacarbazine. Some people whose disease presents with a BRAF gene mutation will receive targeted therapy. NICE technology appraisal 269 recommends vemurafenib as an option for treating locally advanced or metastatic BRAF V600 mutation-positive unresectable or metastatic melanoma. NICE technology appraisal 268 recommends ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy." We would like to note that (1) Since July 23rd 2014, NICE TA319 recommends ipilimumab, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma. Given the availability of ipilimumab and vemurafenib as first-line treatments, we expect that the use of dacarbazine will be very limited. Please consider revising the paragraph accordingly. (2) Not all BRAF mutation positive patients will be treated with a BRAF inhibitor. Some patients may be offered ipilimumab first-line if appropriate (the	Comment noted. The background section in the scope has been updated accordingly.

Section	Consultee/ Commentator	Comments	Action
		use of ipilimumab is not restricted by BRAF mutation status).	
	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	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. First line therapy for advanced melanoma is now rarely dacarbazine. The majority of patients with a BRAF mutation will receive a BRAF inhibitor first line.	Comment noted. The background section in the scope has been updated accordingly.
	Roche Products	We note the absence of a reference to the recent approval by NICE of ipilimumab for the first-line treatment in this indication (TA319). Please note that dacarbazine is no longer regarded as standard of care for first-line treatment of advanced melanoma.	Comment noted. The background section in the scope has been updated accordingly.
The technology/ intervention	British Association of Dermatologists	Yes	Comment noted.
	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	Yes	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Roche Products	Current wording describing the mode of action of pembrolizumab is ambiguous. Suggested changing to: "…antibody involved in both the blockade of immune suppression as well as the subsequent reactivation of anergic T-cells."	Comment noted. The technology section in the scope has been updated accordingly.
Population	British Association of Dermatologists	Yes	Comment noted.
	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	For patients who have received prior therapy other than ipilimumab, MSD does not agree that the proposed population should be restricted to those who have received only 1 prior line of therapy. Consequently, we suggest changing the wording of the population to “People with advanced (unresectable stage III or stage IV) melanoma previously untreated with ipilimumab“. This would match the topic of the appraisal, and would ensure no restriction is made in terms of the number of prior lines of therapy permitted.	Comment noted. It was agreed at the scoping workshop that the population should not be restricted to people who have had only 1 prior line of therapy. The population in the scope has been updated to: ‘People with advanced (unresectable

Section	Consultee/ Commentator	Comments	Action
			stage III or stage IV) melanoma previously untreated with ipilimumab'.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Yes	Comment noted.
	Roche Products	Patients with the BRAF gene mutation should be considered separately. Patients with disease that has metastised to the brain should similarly be considered separately.	Comment noted. The comparators section in the scope lists those comparator technologies for people with BRAF V600 mutation positive. It was agreed at the scoping workshop that people with brain metastases should not be considered separately.
Comparators	British Association of Dermatologists	The comparators are appropriate.	Comment noted. Following the scoping workshop, the comparators in the scope have been updated: temozolomide

Section	Consultee/ Commentator	Comments	Action
			(for people with brain metastases) has been removed and dabrafenib (for people with BRAF V600 mutation-positive disease) has been added to the scope.
	Bristol-Myers Squibb Pharmaceuticals	Ipilimumab should be considered as comparator for both previously untreated and previously treated patients as per NICE TA319 and TA268.	Comment noted. Ipilimumab is listed as a comparator in the scope.
	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 previously untreated with ipilimumab. Given the recent positive NICE guidance for ipilimumab in the first line setting, we suggest it is inappropriate for dacarbazine to be listed as a comparator when considering the population of interest. 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 appraisals by NICE Please note that Temodal (temozolomide) is manufactured by MSD and is not indicated for the treatment of advanced melanoma. MSD agrees that ipilimumab and vemurafenib are appropriate comparators in this appraisal.	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

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			dabrafenib (for people with BRAF V600 mutation-positive disease) has been added to the scope.
	RCP on behalf of NCRI/RCP/RCR /ACP/JCCO	Dacarbazine will only rarely be used in the future as first or 2nd line therapy for melanoma	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.
	Roche Products	No comments	Comment noted.
Outcomes	British Association of Dermatologists	The outcome measures are adequate.	Comment noted.
	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	Agree	Comment noted.
	RCP on behalf	Yes	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	of NCRI/RCP/RCR /ACP/JCCO		
	Roche Products	Yes	Comment noted.
Economic analysis	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	No additional comments	Comment noted.
	Roche Products	The appropriate time horizon for this appraisal is 'lifetime'.	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.
	Bristol-Myers Squibb Pharmaceuticals	No comments	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

Section	Consultee/ Commentator	Comments	Action
			consultation or at the scoping workshop.
	Roche Products	No 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.
	Bristol-Myers Squibb Pharmaceuticals	We do not consider pembrolizumab to be a 'step-change' in the management of melanoma as ipilimumab has already introduced the idea of a check-point inhibitor.	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.

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	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 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 technology offers a step change in the management of advanced 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.
	Roche Products	No comments	Comment noted.
Other considerations	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp &	No additional comments	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Dohme		
	Roche Products	No comments	Comment noted.
NICE Pathways	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 option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy with ipilimumab [proposed STA ID760] , and in people previously untreated with ipilimumab [proposed STA ID ID801]. With regards to the proposed appraisal in people previously untreated with ipilimumab [ID801], we envisage pembrolizumab being used as first and second line treatment options as per the following sequences: • pembrolizumab; ipilimumab • pembrolizumab; vemurafenib • vemurafenib; pembrolizumab; ipilimumab	Comment noted.
Questions for consultation	Bristol-Myers Squibb Pharmaceuticals	No comments	Comment noted.
	Merck Sharp & Dohme	Question: Which treatments are considered to be established clinical practice in the NHS for advanced melanoma in people previously untreated with ipilimumab? Is dacarbazine used at this point in the treatment pathway Response: With the recent publication of TA319: ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (published July 2014), it is expected that ipilimumab will become a standard option for first line therapy. Vemurafenib is also used as first line therapy in BRAF mutation-	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

Section	Consultee/ Commentator	Comments	Action
		positive patients. We do not believe Dacarbazine will continue to be used as a first line treatment option given the availability of ipilimumab in this setting.	should be included in the scope.
	Roche Products	1. Dacarbazine is no longer considered standard of care (following NICE Guidance on vemurafenib (TA269) and ipilimumab (TA268 and TA319). 2. Patients with brain metastases are a clinically meaningful subgroup of patients for whom the cost-effectivess of new drugs may be different compared to the overall patient population. We have no further comments.	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. It was agreed at the scoping workshop that people with brain metastases should not be considered separately.

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

Healthcare Improvement Scotland
Royal College of Pathologists

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab [ID801]

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.	Bristol-Myers Squibb (ipilimumab)	NICE Secretariat		Added	This organisation is a comparator for this appraisal topic. Bristol-Myers Squibb has been added to the matrix of consultees and commentators under 'comparator companies'.
4.	Novartis Pharmaceuticals (dabrafenib)	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'.
5.	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'.

6.	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'
7.	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'.
8.	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'

9.	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'