National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab in combination with ipilimumab for advanced,

unresectable melanoma [ID848]

At the scoping consultation stage, the scopes for nivolumab for treating advanced (unresectable or metastatic) melanoma were considered as 4 separate topics. These are referred to in this document as ID845, ID846, ID847 and ID848, as follows:

- *Nivolumab for treating advanced, unresectable melanoma after progression with anti-CTLA-4 therapy (ID845)*
- *Nivolumab monotherapy for previously untreated, advanced, unresectable melanoma without a BRAF mutation (ID846)*
- *Nivolumab monotherapy for previously untreated, advanced, unresectable BRAF V600 mutation-positive melanoma (ID847)*
- *Nivolumab in combination with ipilimumab for previously untreated, advanced, unresectable melanoma (ID848)*

As nivolumab has now been granted a marketing authorisation, as a monotherapy, for treating advanced (unresectable or metastatic) melanoma in adults, the first 3 of these have been combined to form a single scope for the current appraisal (ID845).Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.

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	Bristol-Myers Squibb	This is an appropriate topic for NICE to consider.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*Would it be appropriate to refer this topic to NICE for appraisal?* Yes	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments		Action
	National Cancer Research Institute/Royal College of Physicians/ Royal College of Radiologists/ Association of Clinical Pathologists (NCRI/RCP/ RCR/ACP)	*Would it be appropriate to refer this topic to NICE for appraisal?*		
		845	Yes	Comment noted. No changes to the scope are needed.
		846	Yes	Comment noted. No changes to the scope are needed.
		847	Yes - the first line trial data currently published compared nivolumab with dacarbazine in BRAF WT patients only. However, it is reasonable to assume that the outcomes would be exactly the same for BRAF mutant melanoma and it is therefore appropriate to seek approval to treat these patients.	Comment noted. No changes to the scope are needed.
		848	This is very premature - the first data evaluating the combination (the 067 trial) has yet to be published in May/June 2015	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal; the timing of this topic will be confirmed.
	Novartis	Yes it would be appropriate to refer this topic to NICE for appraisal.		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Comment noted.

Section	Consultee/ Commentator	Comments	Action
Wording	Bristol-Myers Squibb	The draft remit is appropriate. Please amend the wording in the remit from "advanced, unresectable melanoma" to [redacted] to accurately reflect the expected marketing authorisation.	The remit has been updated to reflect the marketing authorisation.
	British Association of Dermatologists	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	Comment noted. The remit has been updated to reflect the marketing authorisation.
	NCRI/RCP/RCR /ACP	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	Comment noted. The remit has been updated to reflect the marketing authorisation.
	Roche Products	No comment	Comment noted.
Timing Issues	Bristol-Myers Squibb	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 limited treatment options currently available for patients with advanced melanoma.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*What is the relative urgency of this proposed appraisal to the NHS?* ASAP	Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	Survival from advanced melanoma remains poor despite new treatment modalities being introduced recently. More effective treatment is urgently required.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments	Action
	Roche Products	No comment	Comment noted.
Additional comments on the draft remit	British Association of Dermatologists	*Any additional comments on the draft remit* No	Comment noted.
	Roche Products	No comment	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Bristol-Myers Squibb	There is an inconsistency in the proportion of patients with stage III/IV melanoma: In the background of topic 845 it states 10% whereas topics 846,847,848 report 12%. Please consistently use 10% (Ref: National Institute for Health and Clinical Excellence (NICE). Final scope for the appraisal of ipilimumab for previously untreated unresectable malignant melanoma. 2012. Available at: http://www.nice.org.uk/nicemedia/live/12093/61363/61363.pdf) Delete “the” from following text: “There were 11,121 new diagnoses of melanoma in 2011 and 1781 deaths registered in ~~the~~ England in 2012”	The background sections of the scopes have been updated accordingly.
	British Association of Dermatologists	Adequate	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted.
The technology/	Bristol-Myers	845 Please amend description of the technology for scope 845 as	Thank you for your

Section	Consultee/ Commentator	Comments		Action
intervention	Squibb		follows: Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). Nivolumab is capable of blocking inhibitory signalling to T-cells and may activate immune cells and promote an anti-tumour immune response. Nivolumab is administered intravenously. Nivolumab does not currently have a marketing authorisation in the UK for treating advanced melanoma after progression with anti-CTLA-4 therapy. It has been studied in this line of therapy in 1 single arm trial and 1 randomised controlled trial compared with physician's choice of either dacarbazine or carboplatin and paclitaxel in adults without BRAF V600 mutations whose disease has progressed after an anti-CTLA-4 therapy and for those with BRAF V600 mutations, whose disease has progressed after receiving both a BRAF inhibitor and an anti-CTLA-4 therapy.	comment. This section of the scope provides a brief summary of the technology under consideration. This section has been updated to reflect the marketing authorisation.
		846, 847, 848	Please amend description of the technology for scopes 846, 847 and 848 as follows: Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). Nivolumab is capable of blocking inhibitory signalling to T-cells and may activate immune cells and promote an anti-tumour immune response. Nivolumab is administered intravenously.	Thank you for your comment. This section of the scope provides a brief summary of the technology under consideration. This section has been updated to reflect the marketing authorisation.

Section	Consultee/ Commentator	Comments	Action
		Nivolumab does not currently have a marketing authorisation in the UK for treating untreated advanced, (unresectable and metastatic) melanoma. It is being studied as a monotherapy or in combination with ipilimumab compared with ipilimumab alone in people with previously untreated advanced, unresectable melanoma.	
	British Association of Dermatologists	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted
Population	Bristol-Myers Squibb	No subgroups are expected that should be considered separately. Please amend the wording from "advanced, unresectable melanoma" to [redacted] to accurately reflect the expected marketing authorisation.	The population has been updated to reflect the marketing authorisation.
	British Association of Dermatologists	*Is the population defined appropriately?* Yes *Are there any groups within the population that should be considered separately?* No	Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR	*Is the population defined appropriately?*	

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	/ACP	845	This may depend on the licensed indication. Specifically for BRAF mutant melanoma, need to know if previous treatment with both an antiCTLA4 antibody AND a BRAF targeted agent is required.	Comment noted. The population has been amended to reflect the marketing authorisation.
		846, 847, 848	Yes	Comment noted. The population has been amended to reflect the marketing authorisation.
	Roche Products	845	As part of this review, would patients with a BRAF mutation only be considered for nivolumab if they have been previously treated with ipilimumab and a BRAF-targeted therapy? Based on the desire by NICE to stratify the review of nivolumab as an initial therapy by BRAF-mutation status and use with or without ipilimumab, a similar approach may have been anticipated within this review	Comment noted. The population has been amended to reflect the marketing authorisation. Attendees at the scoping workshop considered that it would not be necessary to split the population by BRAF mutation status.
		846	No comment	Comment noted.
		847, 848	The choice of therapy is likely to be influenced by the performance status of the patient, along with the nature of their disease (speed of progression). Such subgroups should be considered as part of this appraisal: please refer to our comments in the 'Comparators' section for further explanation.	Thank you for your comment. Attendees at the scoping workshop highlighted that it would not be easy to identify people with good performance status and slowly progressing

Section	Consultee/ Commentator	Comments		Action
				disease in clinical practice, so this subgroup has not been included in the scope.
Comparators	Bristol-Myers Squibb	845	The comparator listed in the draft scope is representative of the standard treatments used in the NHS. At this line of therapy we would expect BSC to consist of a mix of chemotherapeutic regimens including dacarbazine and paclitaxel/carboplatin combination therapy. Dependent upon the final label received BRAF inhibitors (i.e. vemurafenib and dabrafenib) may also be relevant comparators for people with a BRAF mutation.	Comment noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	Ipilimumab would be the appropriate comparator for people with untreated advanced melanoma without a BRAF mutation. Retreatment with ipilimumab after progression following first-line	Comments noted. Attendees at the scoping workshop

Section	Consultee/ Commentator	Comments		Action
			ipilimumab therapy should not be considered as this would not be in line with the marketing authorisation and is not available in England. Dacarbazine would be considered for people only who are ineligible for, or intolerant to, ipilimumab. Patients who would receive dacarbazine will be identified based on individual clinical opinion.	agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so dacarbazine has been added to the comparators.
		847	Ipilimumab, vemurafenib and dabrafenib would be the appropriate comparators for people with untreated advanced melanoma with a BRAF mutation. The use of ipilimumab in untreated patients is not restricted by BRAF status (see NICE TA319). Dacarbazine would not be considered for these patients given the treatment options available.	Comments noted. No changes to the scope are needed.
		848	The comparators considered should be split by BRAF mutation status as detailed in comments on scopes 846 and 847.	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	British Association of Dermatologists	See comments below		Comments noted.
	NCRI/RCP/RCR /ACP	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared?*		

Section	Consultee/ Commentator	Comments		Action
		845	Should include dacarbazine chemotherapy as well as BSC For BRAF mutant melanoma if previous BRAF targeted therapy is not part of the licensed indication, then vemurafenib and dabrafenib are also relevant comparators.	Comment noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	yes Very few patients are offered cytotoxic chemotherapy as first line therapy nowadays	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been

Section	Consultee/ Commentator	Comments		Action
				added to the comparators.
		847	Yes	Comment noted.
		848	yes Very few patients are offered cytotoxic chemotherapy as first line - probably <5%	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	Roche Products	845	Dacarbazine may be an appropriate comparator for some patients who have progressed following prior treatment with ipilimumab. The draft NICE guideline on 'Melanoma: assessment and management of melanoma' recommends: *"Consider dacarbazine for people with stage 4 metastatic melanoma if immunotherapy or targeted therapy are not suitable. Do not offer further cytotoxic chemotherapy for stage 4 metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial."*	Comment noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator.
		846	No comment	Comment noted.
		847, 848	Depending on the timing of this review and availability of other agents, treatment via BRAF-monotherapy may no longer be the most appropriate comparator. The combination of a BRAF inhibitor (dabrafenib or vemurafenib) with a MEK inhibitor (trametinib or cobimetinib) for patients with a BRAF-mutation should also be considered. We do not believe that ipilimumab is a relevant comparator across all	Attendees at the scoping workshop noted that trametinib is not currently established practice in the NHS. Attendees at the scoping workshop highlighted that it would

Section	Consultee/ Commentator	Comments		Action
			patients considered in this appraisal. Based on discussion at the recent scoping meeting for tamilogene, in conjunction with feedback from other clinical experts, the use of ipilimumab in patients with a BRAF-mutation is increasingly being limited to those patients with a good performance status and more slowly progressing disease. Such subgroups should be considered as part of this appraisal.	not be easy to identify people with good performance status and slowly progressing disease in clinical practice, so this subgroup has not been included in the scope.
Outcomes	Bristol-Myers Squibb	845	The outcomes included in the draft scope are appropriate. [redacted]	Comment noted. No changes to the scope are needed.
		846, 847, 848	The outcomes included in the draft scope are appropriate.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes		Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Comment noted
Economic	Bristol-Myers	As melanoma patients are diagnosed quite young (see background), a life-		Comment noted. The

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analysis	Squibb	time horizon of 40 years is appropriate to reflect any differences in costs or outcomes between the technologies.	reference case stipulates that the time horizon should be long enough to reflect any differences in costs or outcomes between the technologies being compared.
	Roche Products	No comment	Comment noted.
Equality and Diversity	Bristol-Myers Squibb	No equality issues have been identified.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	No	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted
Innovation	Bristol-Myers Squibb	We consider the technology to be innovative. 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 PDL1 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 melanoma. Nivolumab is the anti-PD1 with one of the broadest clinical development program, including more than 35 trials – as monotherapy or in combination with other therapies – in which more than	Comment noted. No changes to the scope are needed.

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		7,000 patients have been enrolled worldwide so far. Nivolumab is currently the PD-1 inhibitor with the most comprehensive and mature clinical data available in advanced melanoma, demonstrating clinically meaningful antitumor activity in two large randomized Phase 3 trials. Nivolumab is the first PD-1 inhibitor with OS data in the Phase III setting. In addition a manageable safety profile was demonstrated in subjects with advanced melanoma, in the context of the observed clinical activity, comparing favourably with the safety profile of current chemotherapies used in advanced disease. Based on available data relating to nivolumab, this is of major interest for public health, in particular from the view point of therapeutic innovation, it has the potential to offer an alternative therapeutic option with an expected improved significant benefit over existing treatments in advanced or metastatic melanoma, a population of a high unmet medical need. The MHRA has issued a Promising Innovative Medicine (PIM) designation for nivolumab in the treatment of advanced (unresectable or metastatic) melanoma in adults in November 2014.		
	British Association of Dermatologists	845	*Do you consider the technology 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)?* Yes it has a reasonably good side effect profile and has been shown in trials to be an effective treatment. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Not sure	Comments noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments		Action
		846, 847, 848	*Do you consider the technology 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)?* Yes *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* We don't think so	Comments noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Do you consider the technology 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)?* Yes		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Noted.
Other considerations	Roche Products	No comment		Noted.
Questions for consultation	British Association of Dermatologists	845	*Have all relevant comparators for nivolumab been included in the scope?* No. *Which treatments are considered to be established clinical practice in the NHS for advanced, unresectable melanoma that has progressed after anti-CTLA-4 therapy?* BRAF inhibitors in patients with a BRAF mutation only, If BRAF wild type there are no	Comments noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator. Following the granting

Section	Consultee/ Commentator	Comments		Action
			established treatments yet. *Would retreatment with ipilimumab be used after progression following first-line ipilimumab therapy?* In some cases. *Is dacarbazine an appropriate comparator for nivolumab in this indication?* No. *Should dabrafenib and vemurafenib be included as comparators for people with BRAF V600 mutation-positive disease who have progressed following treatment?* If progression is after ipilumumab. *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?* Not to our knowledge. *Where do you consider nivolumab will fit into the existing NICE pathway, skin cancer?* Similar to ipilimumab.	of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	*Have all relevant comparators for nivolumab been included in the table?* Yes. *Is dacarbazine an appropriate comparator for people with untreated advanced melanoma without a BRAF mutation?* No. *Would it be considered for certain patient subgroups only (for example, people who are ineligible for, or intolerant to, ipilimumab)?* It could be. *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?* No. *Where do you consider nivolumab will fit into the existing NICE pathway for skin cancer?* Similar to ipilimumab.	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been added to the comparators.

Section	Consultee/ Commentator	Comments		Action
		847	*Have all relevant comparators for nivolumab been included in the table?* No. Mek inhibitors have been excluded from this table e.g. trametinib *Should ipilimumab be included as a comparator for previously untreated disease with a BRAF V600-positive mutation?* Yes. *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?* No. *Where do you consider nivolumab will fit into the existing NICE pathway for skin cancer?* Similar to ipilimumab.	Comments noted. Attendees at the scoping workshop noted that MEK inhibitors (such as trametinib) are not currently established practice in the NHS.
		848	*Have all relevant comparators for nivolumab in combination with ipilimumab been included in the scope?* Again, MEK inhibitors have not been included. *Should ipilimumab be included as a comparator for nivolumab in previously untreated disease with a BRAF V600-positive mutation?* Yes. *Is dacarbazine, or any other chemotherapy, an appropriate comparator for nivolumab in people with untreated advanced unresectable melanoma without a BRAF mutation?* No. *Would it be considered for certain patient subgroups only (for example, people in whom ipilimumab is contraindicated or not tolerated)?* It could be. *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?* No. *Where do you consider nivolumab will fit into the existing NICE*	Comments noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.

Section	Consultee/ Commentator	Comments		Action
			pathway for skin cancer? Similar to ipilimumab.	
	NCRI/RCP/RCR /ACP	845	Commissioning arrangements do not allow retreatment with ipilimumab on progression	Comment noted. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	% pts receiving 1st line dacarbazine or other cytotoxic chemotherapy must be <5%	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been added to the comparators.

Section	Consultee/ Commentator	Comments		Action
	Novartis	*Where do you consider nivolumab will fit into the existing NICE pathway, skin cancer?*		
		845	We anticipate that nivolumab would fit into a) The second-line treatment setting for adults with advanced, unresectable melanoma without the BRAF V600 mutation b) The third-line setting for adults with advanced, unresectable melanoma with the BRAF V600 mutations, whose disease has progressed after receiving both a BRAF inhibitor and an anti-CTLA-4 agent.	Comments noted. No changes to the scope are needed.
		846	We anticipate that nivolumab would fit into the first-line treatment setting for adults with advanced, unresectable melanoma without a BRAF mutation.	Comments noted. No changes to the scope are needed.
		847	We anticipate that nivolumab would fit into the first-line treatment setting for adults with advanced, unresectable BRAF V600 mutation-positive melanoma.	Comments noted. No changes to the scope are needed.
		848	We anticipate that nivolumab in combination with ipilimumab would fit into the first-line treatment setting for adults with advanced, unresectable melanoma with or without a BRAF V600 mutation.	Comments noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	Roche Products	845, 846	- Given the complexity that a review of nivolumab across 4 individual STAs could present to NICE, along with the potential for treatment sequencing, a combined review via the MTA route at time of licence may represent a sensible alternative approach and provide greater	Comments noted. After the scoping workshop, it was agreed to combine ID845, 846 and 847 into

Section	Consultee/ Commentator	Comments		Action
			clarity to the Service on the use of the treatment in clinical practice. - The list of 'related NICE recommendations and NICE Pathways' should be reviewed prior to finalisation of the scope. In January 2015, the Guidance Executive consulted on a proposal to move TA268 to the static list (decision yet to be announced). Furthermore, there may be updates on the proposed review of cobimetinib in combination with vemurafenib [ID 815].	a single scope for nivolumab monotherapy. The list of related NICE recommendations is correct at the time of publication.
		847, 848	- Given the complexity that a review of nivolumab across 4 individual STAs could present to NICE, along with the potential for treatment sequencing, a combined review via the MTA route at time of licence may represent a sensible alternative approach and provide greater clarity to the Service on the use of the treatment in clinical practice. - The list of 'related NICE recommendations and NICE Pathways' should be reviewed prior to finalisation of the scope. In January 2015, the Guidance Executive consulted on a proposal to move TA268 to the static list (decision yet to be announced). Furthermore, there may be updates on the proposed review of cobimetinib in combination with vemurafenib [ID 815]. Please refer to our comments in the 'Population' and 'Comparators' section for detail of subgroups which should be considered as part of this review.	Comments noted. After the scoping workshop, it was agreed to combine ID845, 846 and 847 into a single scope for nivolumab monotherapy; topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal. The list of related NICE recommendations is correct at the time of publication.

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

Royal College of Nursing

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab for treating advanced (unresectable or metastatic) melanoma

At the scoping consultation stage, the scopes for nivolumab for treating advanced (unresectable or metastatic) melanoma were considered as 4 separate topics. These are referred to in this document as ID845, ID846, ID847 and ID848, as follows:

- *Nivolumab for treating advanced, unresectable melanoma after progression with anti-CTLA-4 therapy (ID845)*
- *Nivolumab monotherapy for previously untreated, advanced, unresectable melanoma without a BRAF mutation (ID846)*
- *Nivolumab monotherapy for previously untreated, advanced, unresectable BRAF V600 mutation-positive melanoma (ID847)*
- *Nivolumab in combination with ipilimumab for previously untreated, advanced, unresectable melanoma (ID848)*

As nivolumab has now been granted a marketing authorisation, as a monotherapy, for treating advanced (unresectable or metastatic) melanoma in adults, the first 3 of these have been combined to form a single scope for the current appraisal (ID845).Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.

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	Bristol-Myers Squibb	This is an appropriate topic for NICE to consider.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*Would it be appropriate to refer this topic to NICE for appraisal?* Yes	Comment noted. No changes to the scope are needed.
	National Cancer	*Would it be appropriate to refer this topic to NICE for appraisal?*	

Section	Consultee/ Commentator	Comments		Action
	Research Institute/Royal College of Physicians/ Royal College of Radiologists/ Association of Clinical Pathologists (NCRI/RCP/ RCR/ACP)	845	Yes	Comment noted. No changes to the scope are needed.
		846	Yes	Comment noted. No changes to the scope are needed.
		847	Yes - the first line trial data currently published compared nivolumab with dacarbazine in BRAF WT patients only. However, it is reasonable to assume that the outcomes would be exactly the same for BRAF mutant melanoma and it is therefore appropriate to seek approval to treat these patients.	Comment noted. No changes to the scope are needed.
		848	This is very premature - the first data evaluating the combination (the 067 trial) has yet to be published in May/June 2015	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal; the timing of this topic will be confirmed.
	Novartis	Yes it would be appropriate to refer this topic to NICE for appraisal.		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Comment noted.
Wording	Bristol-Myers Squibb	The draft remit is appropriate. Please amend the wording in the remit from "advanced, unresectable melanoma" to [redacted]		The remit has been updated to reflect the

Section	Consultee/ Commentator	Comments	Action
		[redacted] to accurately reflect the expected marketing authorisation.	marketing authorisation.
	British Association of Dermatologists	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	Comment noted. The remit has been updated to reflect the marketing authorisation.
	NCRI/RCP/RCR /ACP	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	Comment noted. The remit has been updated to reflect the marketing authorisation.
	Roche Products	No comment	Comment noted.
Timing Issues	Bristol-Myers Squibb	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 limited treatment options currently available for patients with advanced melanoma.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*What is the relative urgency of this proposed appraisal to the NHS?* ASAP	Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	Survival from advanced melanoma remains poor despite new treatment modalities being introduced recently. More effective treatment is urgently required.	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted.
Additional comments on the	British Association of	*Any additional comments on the draft remit*	Comment noted.

Section	Consultee/ Commentator	Comments	Action
draft remit	Dermatologists	No	
	Roche Products	No comment	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Bristol-Myers Squibb	There is an inconsistency in the proportion of patients with stage III/IV melanoma: In the background of topic 845 it states 10% whereas topics 846,847,848 report 12%. Please consistently use 10% (Ref: National Institute for Health and Clinical Excellence (NICE). Final scope for the appraisal of ipilimumab for previously untreated unresectable malignant melanoma. 2012. Available at: http://www.nice.org.uk/nicemedia/live/12093/61363/61363.pdf) Delete "the" from following text: "There were 11,121 new diagnoses of melanoma in 2011 and 1781 deaths registered in ~~the~~ England in 2012"	The background sections of the scopes have been updated accordingly.
	British Association of Dermatologists	Adequate	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted.
The technology/ intervention	Bristol-Myers Squibb	845 — Please amend description of the technology for scope 845 as follows: Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). Nivolumab is capable of blocking inhibitory signalling to T-	Thank you for your comment. This section of the scope provides a brief summary of the technology under consideration. This

Section	Consultee/ Commentator	Comments		Action
			cells and may activate immune cells and promote an anti-tumour immune response. Nivolumab is administered intravenously. Nivolumab does not currently have a marketing authorisation in the UK for treating advanced melanoma after progression with anti-CTLA-4 therapy. It has been studied in this line of therapy in 1 single arm trial and 1 randomised controlled trial compared with physician's choice of either dacarbazine or carboplatin and paclitaxel in adults without BRAF V600 mutations whose disease has progressed after an anti-CTLA-4 therapy and for those with BRAF V600 mutations, whose disease has progressed after receiving both a BRAF inhibitor and an anti-CTLA-4 therapy.	section has been updated to reflect the marketing authorisation.
		846, 847, 848	Please amend description of the technology for scopes 846, 847 and 848 as follows: Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). Nivolumab is capable of blocking inhibitory signalling to T-cells and may activate immune cells and promote an anti-tumour immune response. Nivolumab is administered intravenously. Nivolumab does not currently have a marketing authorisation in the UK for treating untreated advanced, (unresectable and metastatic) melanoma. It is being studied as a monotherapy or in combination with ipilimumab compared with ipilimumab alone in people with previously untreated advanced, unresectable melanoma.	Thank you for your comment. This section of the scope provides a brief summary of the technology under consideration. This section has been updated to reflect the marketing authorisation.

Section	Consultee/ Commentator	Comments		Action
	British Association of Dermatologists	*Is the description of the technology or technologies accurate?* Yes		Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Is the description of the technology or technologies accurate?* Yes		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Comment noted
Population	Bristol-Myers Squibb	No subgroups are expected that should be considered separately. Please amend the wording from "advanced, unresectable melanoma" to [redacted] to accurately reflect the expected marketing authorisation.		The population has been updated to reflect the marketing authorisation.
	British Association of Dermatologists	*Is the population defined appropriately?* Yes *Are there any groups within the population that should be considered separately?* No		Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Is the population defined appropriately?*		
		845	This may depend on the licensed indication. Specifically for BRAF mutant melanoma, need to know if previous treatment with both an antiCTLA4 antibody AND a BRAF targeted agent is required.	Comment noted. The population has been amended to reflect the marketing authorisation.
		846, 847,	Yes	Comment noted. The population has been

Section	Consultee/ Commentator	Comments		Action
		848		amended to reflect the marketing authorisation.
	Roche Products	845	As part of this review, would patients with a BRAF mutation only be considered for nivolumab if they have been previously treated with ipilimumab and a BRAF-targeted therapy? Based on the desire by NICE to stratify the review of nivolumab as an initial therapy by BRAF-mutation status and use with or without ipilimumab, a similar approach may have been anticipated within this review	Comment noted. The population has been amended to reflect the marketing authorisation. Attendees at the scoping workshop considered that it would not be necessary to split the population by BRAF mutation status.
		846	No comment	Comment noted.
		847, 848	The choice of therapy is likely to be influenced by the performance status of the patient, along with the nature of their disease (speed of progression). Such subgroups should be considered as part of this appraisal: please refer to our comments in the 'Comparators' section for further explanation.	Thank you for your comment. Attendees at the scoping workshop highlighted that it would not be easy to identify people with good performance status and slowly progressing disease in clinical practice, so this subgroup has not been included in the scope.
Comparators	Bristol-Myers Squibb	845	The comparator listed in the draft scope is representative of the standard treatments used in the NHS. At this line of therapy we would expect BSC to consist of a mix of	Comment noted. Attendees at the scoping workshop

Section	Consultee/ Commentator	Comments		Action
			chemotherapeutic regimens including dacarbazine and paclitaxel/carboplatin combination therapy. Dependent upon the final label received BRAF inhibitors (i.e. vemurafenib and dabrafenib) may also be relevant comparators for people with a BRAF mutation.	agreed that dacarbazine is an appropriate comparator. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	Ipilimumab would be the appropriate comparator for people with untreated advanced melanoma without a BRAF mutation. Retreatment with ipilimumab after progression following first-line ipilimumab therapy should not be considered as this would not be in line with the marketing authorisation and is not available in England. Dacarbazine would be considered for people only who are ineligible for, or intolerant to, ipilimumab. Patients who would receive dacarbazine will be identified based on individual clinical opinion.	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so dacarbazine has been added to the comparators.

Section	Consultee/ Commentator	Comments		Action
		847	Ipilimumab, vemurafenib and dabrafenib would be the appropriate comparators for people with untreated advanced melanoma with a BRAF mutation. The use of ipilimumab in untreated patients is not restricted by BRAF status (see NICE TA319). Dacarbazine would not be considered for these patients given the treatment options available.	Comments noted. No changes to the scope are needed.
		848	The comparators considered should be split by BRAF mutation status as detailed in comments on scopes 846 and 847.	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	British Association of Dermatologists	See comments below		Comments noted.
	NCRI/RCP/RCR /ACP	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared?*		
		845	Should include dacarbazine chemotherapy as well as BSC For BRAF mutant melanoma if previous BRAF targeted therapy is not part of the licensed indication, then vemurafenib and dabrafenib are also relevant comparators.	Comment noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator. Following the granting of a marketing authorisation, which

Section	Consultee/ Commentator	Comments		Action
				does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	yes Very few patients are offered cytotoxic chemotherapy as first line therapy nowadays	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been added to the comparators.
		847	Yes	Comment noted.
		848	yes Very few patients are offered cytotoxic chemotherapy as first line - probably <5%	Comment noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate

Section	Consultee/ Commentator	Comments		Action
				appraisal.
	Roche Products	845	Dacarbazine may be an appropriate comparator for some patients who have progressed following prior treatment with ipilimumab. The draft NICE guideline on 'Melanoma: assessment and management of melanoma' recommends: *"Consider dacarbazine for people with stage 4 metastatic melanoma if immunotherapy or targeted therapy are not suitable. Do not offer further cytotoxic chemotherapy for stage 4 metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial."*	Comment noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator.
		846	No comment	Comment noted.
		847, 848	Depending on the timing of this review and availability of other agents, treatment via BRAF-monotherapy may no longer be the most appropriate comparator. The combination of a BRAF inhibitor (dabrafenib or vemurafenib) with a MEK inhibitor (trametinib or cobimetinib) for patients with a BRAF-mutation should also be considered. We do not believe that ipilimumab is a relevant comparator across all patients considered in this appraisal. Based on discussion at the recent scoping meeting for tamilogene, in conjunction with feedback from other clinical experts, the use of ipilimumab in patients with a BRAF-mutation is increasingly being limited to those patients with a good performance status and more slowly progressing disease. Such subgroups should be considered as part of this appraisal.	Attendees at the scoping workshop noted that trametinib is not currently established practice in the NHS. Attendees at the scoping workshop highlighted that it would not be easy to identify people with good performance status and slowly progressing disease in clinical practice, so this subgroup has not been included in the scope.

Section	Consultee/ Commentator	Comments		Action
Outcomes	Bristol-Myers Squibb	845	The outcomes included in the draft scope are appropriate. [redacted]	Comment noted. No changes to the scope are needed.
		846, 847, 848	The outcomes included in the draft scope are appropriate.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes		Comment noted. No changes to the scope are needed.
	NCRI/RCP/RCR /ACP	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Comment noted
Economic analysis	Bristol-Myers Squibb	As melanoma patients are diagnosed quite young (see background), a life-time horizon of 40 years is appropriate to reflect any differences in costs or outcomes between the technologies.		Comment noted. The reference case stipulates that the time horizon should be long enough to reflect any differences in costs or outcomes between the technologies being compared.

Section	Consultee/ Commentator	Comments	Action
	Roche Products	No comment	Comment noted.
Equality and Diversity	Bristol-Myers Squibb	No equality issues have been identified.	Comment noted. No changes to the scope are needed.
	British Association of Dermatologists	No	Comment noted. No changes to the scope are needed.
	Roche Products	No comment	Comment noted
Innovation	Bristol-Myers Squibb	We consider the technology to be innovative. 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 PDL1 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 melanoma. Nivolumab is the anti-PD1 with one of the broadest clinical development program, including more than 35 trials – as monotherapy or in combination with other therapies – in which more than 7,000 patients have been enrolled worldwide so far. Nivolumab is currently the PD-1 inhibitor with the most comprehensive and mature clinical data available in advanced melanoma, demonstrating clinically meaningful antitumor activity in two large randomized Phase 3 trials. Nivolumab is the first PD-1 inhibitor with OS data in the Phase III setting. In addition a manageable safety profile was demonstrated in subjects with advanced melanoma, in the context of the observed clinical activity, comparing favourably with the safety profile of current chemotherapies used in advanced disease.	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments		Action
		Based on available data relating to nivolumab, this is of major interest for public health, in particular from the view point of therapeutic innovation, it has the potential to offer an alternative therapeutic option with an expected improved significant benefit over existing treatments in advanced or metastatic melanoma, a population of a high unmet medical need. The MHRA has issued a Promising Innovative Medicine (PIM) designation for nivolumab in the treatment of advanced (unresectable or metastatic) melanoma in adults in November 2014.		
	British Association of Dermatologists	845	*Do you consider the technology 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)?* Yes it has a reasonably good side effect profile and has been shown in trials to be an effective treatment. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Not sure	Comments noted. No changes to the scope are needed.
		846, 847, 848	*Do you consider the technology 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)?* Yes *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* We don't think so	Comments noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments		Action
	NCRI/RCP/RCR /ACP	*Do you consider the technology 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)?* Yes		Comment noted. No changes to the scope are needed.
	Roche Products	No comment		Noted.
Other considerations	Roche Products	No comment		Noted.
Questions for consultation	British Association of Dermatologists	845	*Have all relevant comparators for nivolumab been included in the scope?* No. *Which treatments are considered to be established clinical practice in the NHS for advanced, unresectable melanoma that has progressed after anti-CTLA-4 therapy?* BRAF inhibitors in patients with a BRAF mutation only, If BRAF wild type there are no established treatments yet. *Would retreatment with ipilimumab be used after progression following first-line ipilimumab therapy?* In some cases. *Is dacarbazine an appropriate comparator for nivolumab in this indication?* No. *Should dabrafenib and vemurafenib be included as comparators for people with BRAF V600 mutation-positive disease who have progressed following treatment?* If progression is after ipilumumab. *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?* Not to our knowledge.	Comments noted. Attendees at the scoping workshop agreed that dacarbazine is an appropriate comparator. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for people with previously treated melanoma – that is, BRAF inhibitors,

Section	Consultee/ Commentator	Comments		Action
			Where do you consider nivolumab will fit into the existing NICE pathway, skin cancer? Similar to ipilimumab.	ipilimumab, dacarbazine and best supportive care.
		846	*Have all relevant comparators for nivolumab been included in the table?* Yes. *Is dacarbazine an appropriate comparator for people with untreated advanced melanoma without a BRAF mutation?* No. *Would it be considered for certain patient subgroups only (for example, people who are ineligible for, or intolerant to, ipilimumab)?* It could be. *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?* No. *Where do you consider nivolumab will fit into the existing NICE pathway for skin cancer?* Similar to ipilimumab.	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been added to the comparators.
		847	*Have all relevant comparators for nivolumab been included in the table?* No. Mek inhibitors have been excluded from this table e.g. trametinib *Should ipilimumab be included as a comparator for previously untreated disease with a BRAF V600-positive mutation?* Yes. *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?* No. *Where do you consider nivolumab will fit into the existing NICE pathway for skin cancer?* Similar to ipilimumab.	Comments noted. Attendees at the scoping workshop noted that MEK inhibitors (such as trametinib) are not currently established practice in the NHS.

Section	Consultee/ Commentator	Comments		Action
		848	*Have all relevant comparators for nivolumab in combination with ipilimumab been included in the scope?* Again, MEK inhibitors have not been included. *Should ipilimumab be included as a comparator for nivolumab in previously untreated disease with a BRAF V600-positive mutation?* Yes. *Is dacarbazine, or any other chemotherapy, an appropriate comparator for nivolumab in people with untreated advanced unresectable melanoma without a BRAF mutation?* No. *Would it be considered for certain patient subgroups only (for example, people in whom ipilimumab is contraindicated or not tolerated)?* It could be. *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?* No. *Where do you consider nivolumab will fit into the existing NICE pathway for skin cancer?* Similar to ipilimumab.	Comments noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	NCRI/RCP/RCR /ACP	845	Commissioning arrangements do not allow retreatment with ipilimumab on progression	Comment noted. Following the granting of a marketing authorisation, which does not specify particular previous treatments, the comparators have been updated to include all treatment options that may be considered for

Section	Consultee/ Commentator	Comments		Action
				people with previously treated melanoma – that is, BRAF inhibitors, ipilimumab, dacarbazine and best supportive care.
		846	% pts receiving 1st line dacarbazine or other cytotoxic chemotherapy must be <5%	Comments noted. Attendees at the scoping workshop agreed that dacarbazine would be considered in people for whom ipilimumab is unsuitable, so has been added to the comparators.
	Novartis	*Where do you consider nivolumab will fit into the existing NICE pathway, skin cancer?*		
		845	We anticipate that nivolumab would fit into a) The second-line treatment setting for adults with advanced, unresectable melanoma without the BRAF V600 mutation b) The third-line setting for adults with advanced, unresectable melanoma with the BRAF V600 mutations, whose disease has progressed after receiving both a BRAF inhibitor and an anti-CTLA-4 agent.	Comments noted. No changes to the scope are needed.
		846	We anticipate that nivolumab would fit into the first-line treatment setting for adults with advanced, unresectable melanoma without a	Comments noted. No changes to the scope

Section	Consultee/ Commentator	Comments		Action
			BRAF mutation.	are needed.
		847	We anticipate that nivolumab would fit into the first-line treatment setting for adults with advanced, unresectable BRAF V600 mutation-positive melanoma.	Comments noted. No changes to the scope are needed.
		848	We anticipate that nivolumab in combination with ipilimumab would fit into the first-line treatment setting for adults with advanced, unresectable melanoma with or without a BRAF V600 mutation.	Comments noted. Topic ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal.
	Roche Products	845, 846	- Given the complexity that a review of nivolumab across 4 individual STAs could present to NICE, along with the potential for treatment sequencing, a combined review via the MTA route at time of licence may represent a sensible alternative approach and provide greater clarity to the Service on the use of the treatment in clinical practice. - The list of 'related NICE recommendations and NICE Pathways' should be reviewed prior to finalisation of the scope. In January 2015, the Guidance Executive consulted on a proposal to move TA268 to the static list (decision yet to be announced). Furthermore, there may be updates on the proposed review of cobimetinib in combination with vemurafenib [ID 815].	Comments noted. After the scoping workshop, it was agreed to combine ID845, 846 and 847 into a single scope for nivolumab monotherapy. The list of related NICE recommendations is correct at the time of publication.
		847, 848	- Given the complexity that a review of nivolumab across 4 individual STAs could present to NICE, along with the potential for treatment sequencing, a combined review via the MTA route at time of licence may represent a sensible alternative approach and provide greater clarity to the Service on the use of the treatment in clinical practice. - The list of 'related NICE recommendations and NICE Pathways'	Comments noted. After the scoping workshop, it was agreed to combine ID845, 846 and 847 into a single scope for nivolumab monotherapy; topic

Section	Consultee/ Commentator	Comments		Action
			should be reviewed prior to finalisation of the scope. In January 2015, the Guidance Executive consulted on a proposal to move TA268 to the static list (decision yet to be announced). Furthermore, there may be updates on the proposed review of cobimetinib in combination with vemurafenib [ID 815]. Please refer to our comments in the 'Population' and 'Comparators' section for detail of subgroups which should be considered as part of this review.	ID848 (nivolumab in combination with ipilimumab) will be the subject of a separate appraisal. The list of related NICE recommendations is correct at the time of publication.

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

Royal College of Nursing