National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma

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	Roche Products	We agree that this is an appropriate topic for consideration by NICE.	Thank you for your comment.
	Melanoma Focus	This is an appropriate referral	Thank you for your comment.
Wording	Roche Products	The wording of the remit is accurate and appropriate.	Thank you for your comment.
	Melanoma Focus	We might highlight that what is being discussed here is cutaneous melanoma as opposed to melanoma that start in mucous membranes, the eye or CNS. The technology appraisal should not be limited to vemurafenib plus cobimetenib but should recognise the competing combination with the same targets dabrafenib and vemurafenib which looks at least as effective with a larger dataset and which is going through NICE appraisal in autumn 2015.	Thank you for your comments. The background section of the scope explains in the first paragraph that this topic relates to the skin. This appraisal will be scheduled in line with

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			the expected marketing authorisation dates. Any subsequent topics will be appraised in line with their respective marketing authorisation dates.
Timing	Melanoma Focus	This is urgent. Combination Braf and MEK directed therapy has been demonstrated to be advantageous in terms of survival. Very many patients have been treated on trials and expanded access schemes and subsequent patients are currently disadvantaged through not having access to combination therapy.	Thank you for your comment. The timing of this appraisal will be scheduled in line with the expected marketing authorisation dates. Please see section 2.5.19 of the NICE guide to the process of technology appraisal for further details. http://www.nice.org.uk/article/pmg19/chapter/2-selection-of-technologies#developing-the-remit-and-scope

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Roche Products	RAS/MAPK" is not defined in the third paragraph of this section, although 'The technology' section later refers to mitogen-actived protein kinases (MAPK). It may be helpful to define these terms in the Background section, along with BRAF. The third paragraph states that the BRAF V600 mutation is found in approximately 50% of all melanomas. We believe this to be an over-estimate, with a recent study reporting a mutation rate of 43% in stage IV patients in Germany [Heinzerling, Br J Cancer, 2013;108:2164-71]. There is no reason to suspect a different rate of mutation presence between German and UK patients. The fourth paragraph describes the NICE recommendations of TA269 and TA321, and that these are contingent on "the companies provid[ing] them with the discount agreed in the patient access scheme". It would be more accurate to refer to there being two distinct and separate patient access schemes being available for vemurafenib and dabrafenib. Similarly, the text could be adjusted from "as an option for treating" to "as options for treating".	Thank you for your comments. The background section provides only a general overview of the disease area. The prevalence of BRAF cited in the NICE scope is an approximation which is referenced in a range of literature including the National Institute for Health Research briefing paper: http://www.hsc.nihr.ac.uk/topics/vemurafenib-and-cobimetinib-for-previously-untreat/
	Melanoma Focus	This is brief but sufficient. You might consider recognising the difference between MAPK-directed therapy (requires mutation, works quickly, curently does not lead lo long term survival advantage) versus ipilimumab (all patients, works slowly for minority but for these few offers long term survival advantage). You should also recognise the imminent licensing of nivolumab and probably pembrolizumab, very effective immunotherapies.	Thank you for your comment. The background section provides only a general overview of the disease area.
The technology/	Roche Products	It may be helpful to define MEK in this section of the scope.	Thank you for your comment. The

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intervention			technology section provides only a general overview.
	Melanoma Focus	The background should make mention of the recently published data Robert 2015 PMID 25399551, Long 2014 PMID 25265492, Larkin 2015 PMID 25265494 looking at this and the competing combination	Thank you for your comment. The technology section provides only a general overview.
Population	Roche Products	We consider the Population description to be accurate.	Thank you for your comment.
	Melanoma Focus	Yes	Thank you for your comment.
Comparators	Roche Products	We believe the comparators listed in this section - dabrafenib and vemurafenib - to be appropriate and complete, when considering the management of patients with BRAF V600 mutation-positive melanoma. To respond to the later 'Question for consultation', dacarbazine and ipilimumab are not relevant comparators in this assessment. Please see our response below for a fuller explanation on this point.	Thank you for your comment.
	British Association of Dermatologists	A legitimate comparator would be ipilimumab combined with a PD-1 inhibitor but we accept that it may be too early to consider this combination, and this question reflects the difficulty of considering novel therapies when they are in a state of rapid evolution.	Thank you for your comment. NICE can only consider comparators that are established clinical

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			practice within the NHS.
	Melanoma Focus	Either vemurafenib or dabrafenib are appropriate standard comparators	Thank you for your comment.
Outcomes	Melanoma Focus	A measure of short term health gains from rapid response would be valuable, including people continuing to work, caring for families etc. Additionally, the outcomes should reflect the reduced incidence of skin toxicities including new cancers on the combination arm.	Thank you for your comment. These outcome measures are already included as part of the current list defined in the NICE scope.
Other considerations	Melanoma Focus	The combination of dabrafenib and trametenib should be recognsied in this appraisal as it is virtually the same technology with better data and NICE appraisal is scheduled for autumn 2015.	Thank you for your comment. NICE can only consider comparators that are established practice within the NHS.
Innovation	Roche Products	The combination of cobimetinib and vemurafenib is a further step-change in the management of BRAF V600 mutation-positive advanced melanoma, adding to the significant improvement in progression free survival, overall survival and health-related quality of life already seen with vemurafenib. There is a strong scientific and clinical rationale for the the addition cobimetinib to vemurafenib, with the added mechanism of action offering inhibition of MEK, which acts on the same MAPK signalling pathway vemurafenib.	Thank you for your comment.
	Melanoma	The combination of cobimetenib + vemurafanib OR trametenib + dabrafenib	Thank you for your

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	Focus	appear to represent a significant step change improvement with higher probability and longer duration of response, longer PFS and longer OS compared to single agent therapy. At this point in a rapidly changing field, this improvement can make a major difference in allowing fit patients to continue for longer working and caring for dependents as well as potentially allowing them access to future improved immunotherapy options that look like impacting on long term survival.	comment.
Questions for consultation	Roche Products	Dacarbazine is no longer a standard of care in the first line management of patients with BRAF V600 mutation-positive advanced melanoma, and does not represent a comparator to cobimetinib + vemurafenib in this population. This view was also discussed at the recent scoping workshop for tamilogene laherparepvec for the treatment of metastatic melanoma. Ipilimumab is also not a relevant comparator in this appraisal. Cobimetinib represents a first-line add-on treatment to the current standard of care in BRAF V600 mutation-positive patients (vemurafenib), in patients where the decision has already been made to use BRAF-directed therapy. We believe that cobimetinib would be used in combination with vemurafenib, with the treatments being co-initiated in patients with previously untreated advanced melanoma. We agree the STA process is the appropriate process for this appraisal.	Thank you for your comment.
	GlaxoSmithKline	Have all relevant comparators for cobimetinib been included in the scope? A. Yes all relevant comparators have been included in the scope. Q. Are ipilimumab or dacarbazine appropriate comparators for this patient population? A. Although ipilimumab could be used, a BRAF inhibitor is the current	Thank you for your comment.

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments</th><th>Action</th></tr>
<tr><td></td><td></td><td>standard of care for this patient population. There is no evidence network availabe to inform a comparison versus ipilimumab in the 1L BRAF mutation-positive population.

Given the availability of BRAF inhibitors dacarbazine is no longer a relevant 1L treatment for BRAF mutation-positive patients. This was confirmed by clinical experts during the recent appraisal of dabrafenib (TA 321).</td><td></td></tr>
<tr><td></td><td>Melanoma Focus</td><td>Have all relevant comparators for cobimetinib been included in the scope? Are ipilimumab or dacarbazine appropriate comparators for this patient population?

Treatments for advanced melanoma
<table>
<tr><th>Treatment</th><th>Current status</th><th>Population / pathway</th><th>Outcomes</th><th>Appropriate comparator for cobimetinib+vemurafenib?</th><th>Reference / data source</th></tr>
<tr><td>Ipilimumab – anti-CTLA4</td><td>Licensed and NICE approved,</td><td>All patients regardless of mutation status, no predictive biomarkers</td><td>Median OS 10.1m (8.0-13.8^) vs 6.4m (5.5-8.7) for a vaccine presumed inactive. 24m OS 23.5% vs 13.7%</td><td>No. Ipilimumab would be used in sequence before or after MAPK directed therapy*. Population is not mutation defined.</td><td>Hodi 2010 PMID 20525992</td></tr>
<tr><td>Nivolumab – anti-PD1</td><td>Not licensed in UK, not clear</td><td>All patients regardless of</td><td>1-year OS 73% vs 42% (DTIC),</td><td>No. Nivolumab would be used in sequence before or after MAPK directed</td><td>Robert 2015 PMID 253995</td></tr>
</table></td><td>Thank you for your comments and additional information to support the choice of comparators, outcomes and wording for the background of this scope.</td></tr>
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Section	Consultee/ Commentator	Comments						Action
			when NICE review scheduled	mutation status	ORR 40% vs 14%	therapy not as an alternative.	52	
		Vemurafenib – inhibitor of mutated Braf	Licensed and NICE approved	Patients with Braf 600 mutation (efficacy applies to 600E and 600K mutation)	Median OS 1.6m (12.0-15.2) vs 9.7m (7.9-12.8) for DTIC. OS curves converge by 2 years. ORR 57% vs9%.	Yes – can be considered a standard of care for same mutation-defined population	McArthur 2014 PMID 24508103	
		Dabrafenib – inhibitor of mutated Braf	Licensed and NICE approved	Patients with Braf 600 mutation	Median PFS 5.1m vs 2.7m for DTIC, ORR 50% vs 6%.	Yes – can be considered a standard of care for same mutation-defined population	Hauschild 2012 PMID 22735384	
		Cobinetinib – inhibitor of MEK	Not licensed	Patients with Braf 600 mutation	Data not found	No – single agent MEK inhibition is an active treatment in this mutation-selected population if not previously exposed to Braf inhibition but not as active as Braf therapy. There is a case to be made for sequential MEK-inhibition followed by		
		Trametenib – inhibitor of MEK	Licensed as monotherapy	Patients with Braf 600 mutation	HR death trametenib vs DTIC 0.54 (0.32-0.92), 6m OS 81% vs 67%, ORR 22%		Flaherty 2012 PMID 22663011	

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					vs 8%	Braf-inhibition as an alternative to combination treatment. But sequential treatment is not tested in trials and neither MEK inhibitor is currently funded as monotherapy.		
		Dabrafenib +trametenib	Not licensed	Patients with Braf 600 mutation	Median OS not reached vs 17.2 vemurafenib, 12m OS 72% (67-77) vs 65% (59-70), ORR 64% vs 51%. HR death dab+tram vs dab 0.63 (0.42-0.94), 6m OS 93% vs 85%, ORR 67% vs 51%	Yes – this combination has been widely available on expanded access programme with good outcomes. Unofficially was widely regarded as standard of care until programme closed 20/01/2015	Robert 2015 PMID 25399551 Long 2014 PMID 25265492	
		Vemurafenib + Cobinetinib	Not licensed	Patients with Braf 600 mutation	9m OS 81% vs 73% vemurafe	N/A	Larkin 2015 PMID 252654	

Section	Consultee/ Commentator	Comments	Action

			nib, HR death 0.65 (0.42-1.00), ORR 68% vs 45%		94
Dacarbazine (DTIC) – cytotoxic chemotherapy	Licensed	All patients regardless of mutation status, no predictive biomarkers	See control arms above	No. Unproven survival benefit compared to no treatment, proven to be outperformed in this population by MAPK-directed treatment, might be used in sequence with other agents, not as alternative	
Paclitaxel+carboplatin - cytotoxic chemotherapy			Median OS 42w, ORR 12%		Hauschild 2009 19349552

* MAPK pathway is the signalling cascade which when activated can drive proliferation and promote survival of malignant cells. Components of that pathway include mutated Braf (target for vemurafenib and dabrafenib) and non-mutated MEK downstream of Braf (targets for trametenib and cobimetinib). Drugs targeting any component of this pathway are MAPK-directed therapy.
^ 95%CI

Which treatments are considered to be established clinical practice in the NHS for treating BRAF V600 mutation positive unresectable locally advanced or metastatic melanoma?

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		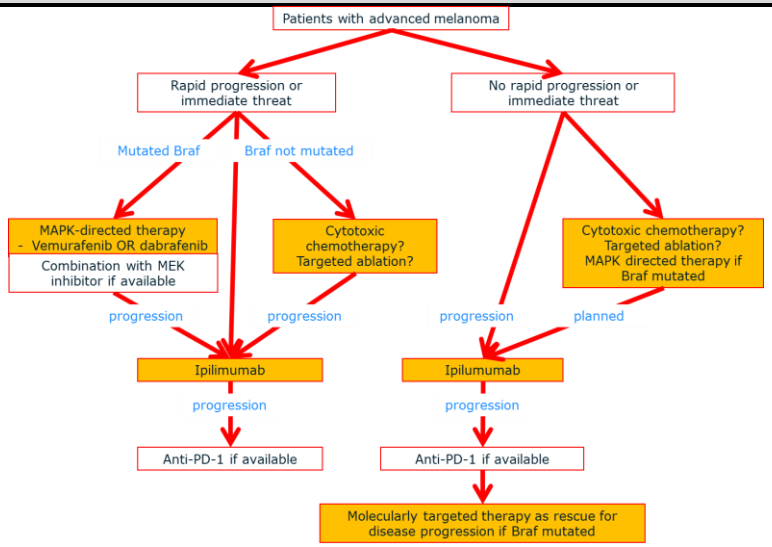 Treatments marked in orange are licensed and NICE approved for funding. ***Are there any subgroups of people in whom cobimetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No Subgroup analysis did not suggest greater benefit in any group within the mutated Braf melanoma cohort. ***Where do you consider cobimetinib will fit into the existing NICE pathway, for skin cancer?*** See above Cobimetenib+vemurafenib OR dabrafenib + trametenib should be considered standard of care for patients with advanced melanoma with Braf mutation	

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		who have disease that is rapidly progressive, high volume, threatening a specific organ or that has progressed after immune therapy. However, NICE guidance should not be restrict its use to these conditions but allow the clinician to determine its place in the complex pathway. Cobimetinib might be considered as single agent therapy for patients with advanced melanoma carrying mutated Braf, intolerant of Braf inhibition but whose disease has not progressed on a Braf inhibitor. ***Will the proposed remit and scope:*** **exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cobimetinib will be licensed;** No **lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** No **could have any adverse impact on people with a particular disability or disabilities.** No ***Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*** Not applicable ***Do you consider cobimetinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?***	

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		The combination of cobimetenib + vemurafanib OR trametenib+ dabrafenib appear to represent a significant step change improvement with higher probability and longer duration of response, longer PFS and longer OS compared to single agent therapy. At this point in a rapidly changing field, this improvement can make a major difference in allowing fit patients to continue for longer working and caring for dependents as well as potentially allowing them access to future improved immunotherapy options that look like impacting on long term survival. ***Do you consider that the use of cobimetinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*** These MAPK-directed therapies result in rapid reduction in tumour volume and dramatic improvements in short term quality of life (starting within days of treatment commencing in many cases) irrespective of survival data. The combined treatment strategies have a higher probability of response and better toxicity profile and so offer a short term significant improvement in quality of life. Clinical experience indicates that the return of patients to near normal health and their working, bringing up family etc are commonly observed improvements in quality of life for people on this treatment that have been poorly captured by existing data.	

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

Department of Health
British Association of Skin Cancer Specialist Nurses

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology (STA)

Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

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	Afiya Trust	NICE Secretariat		Removed	This organisation is no longer active to engage in NICE topics. Afiya Trust has been removed from the list of matrices "under patient group"
2	Muslim Network Council	NICE Secretariat		Removed	This organisation has disbanded. Muslim Network Council has been removed from the list of matrices under "patient group"