National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

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

Section	Consultee/ Commentator	Comments	Action
Background information	Novartis	No comments	Noted. No changes to the scope are needed.
The technology/ intervention *[Is the description of the technology or technologies accurate?]*	British Association of Dermatologists	Yes	Comment noted. No changes to the scope are needed.
	Novartis	Yes its accurate	Comment noted. No changes to the scope are needed.
	Roche Products	As stated within the draft scope, trametinib is licensed as both a monotherapy treatment option, and in combination with dabrafenib, for use in patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The proposed scope does not include an assessment of trametinib monotherapy, and to date there has been no guidance or statement issued by NICE on trametinib use as a monotherapy agent. We are concerned that a lack of any form of NICE guidance, advice, or statement could cause confusion on the status of trametinib monotherapy, particularly when considering the international reach of NICE, and users of its guidance who	Thank you for your comment. NICE has not received a referral from the Department of Health, to appraise trametinib as a monotherapy. Trametinib monotherapy is

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		may not fully understand the rationale behind the lack of any guidance. Recognising it is outside the scope of NICE to appraise technologies which have not been referred, we would ask if NICE intend to publish an Evidence Summary on the status of trametinib monotherapy to help provide this clarity?	therefore not included in this appraisal, and no appraisal is currently scheduled. An Evidence Summary on trametinib monotherapy is not currently in development; details of published and developing NICE advice can be found on our website, http://www.nice.org.uk/advice/.
Population *[Is the population defined appropriately?]*	British Association of Dermatologists	Yes	Comment noted. No changes to the scope are needed.
	Novartis	Yes, population defined appropriately	Comment noted. No changes to the scope are needed.
	Roche Products	Appropriate	Comment noted. No changes to the scope are needed.
Comparators	British Association of	Yes	Comment noted. No changes to the scope

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[Are these the standard treatments currently used in the NHS with which the technology should be compared?]	Dermatologists		are needed.
	Novartis	Yes, the comparators are the treatments currently used in NHS	Comment noted. No changes to the scope are needed.
	Roche Products	Appropriate	Comment noted. No changes to the scope are needed.
Outcomes *[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]*	British Association of Dermatologists	Yes	Comment noted. No changes to the scope are needed.
	Novartis	Yes, the outcomes capture the most important benefits of the technology	Comment noted. No changes to the scope are needed.
	Roche Products	Appropriate	Comment noted. No changes to the scope are needed.
Economic analysis	British Association of Dermatologists	No specific time line i.e. months/years is stipulated and therefore leaves this area open to enable the most appropriate economic analysis, which I think is reasonable, especially in view of the relatively short follow-up data available.	Comment noted. No changes to the scope are needed.
	Novartis	The economic analysis will be based on a lifetime horizon as per NICE guidance	Comment noted. No changes to the scope are needed.

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	Roche Products	Appropriate	Comment noted. No changes to the scope are needed.
Equality and Diversity	British Association of Dermatologists	No issues	Comment noted. No changes to the scope are needed.
	Novartis	None identified	Comment noted. No changes to the scope are needed.
Innovation *[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)?]*	British Association of Dermatologists	Yes As mentioned above, less toxicity.	Comment noted. No changes to the scope are needed.
	Novartis	The innovative combination of a MEK inhibitor with a BRAF inhibitor promises to deliver a step-change advancement in the treatment of patients with BRAFV600 mutation positive metastatic melanoma, over and above that offered by the current standard of care (targeted BRAF inhibitor monotherapy) for the following reasons: The typical development of resistance to monotherapy BRAF inhibition due to signal transduction along alternative pathways to stimulate MEK and then ERK with eventual cell proliferation, has limited median progression-free survival to around 7 months. There is currently a paucity of available licensed treatment options for second line treatment for these patients. Ipilimumab is slow to have an effect and this only occurs unpredictably in a minority of patients, although the effect is durable.	Comment noted. No changes to the scope are needed.

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		Our improved understanding of the MAPK pathway and mechanisms of resistance has both led to the rapid development (within 4 years) of the novel MEK inhibitor, trametinib as well as its study in combination with dabrafenib. The combination of dabrafenib and trametinib has substantially increased PFS and OS, and increased RR by around 50%, with patients achieving at least complete stabilisation of disease, relative to BRAF inhibitor monotherapy efficacy. The combination of dabrafenib and trametinib shows substantially less skin toxicity than vemurafenib, although there are some unique toxicities associated with combination therapy that have been shown to be manageable. The combination of dabrafenib and trametinib meets the end of life criteria by offering an extension to life of at least three additional months versus vemurafenib and dabrafenib – the current standards of care. The patient population with BRAF V600 mutation positive melanoma is small and has a median life expectancy of less than 24 months where there is no alternative treatment of comparable benefit. The assessment of this medicine under these criteria makes allowances for some of the benefit that may not be captured in the QALY for patients with a severe disease and a short life expectancy.	
Other considerations	British Association of Dermatologists	It is well recognised that combination treatment leads to less side effects especially cutaneous toxicity and therefore less need for other specialist healthcare input and investigations such as biopsy extra tests etc. It perhaps is difficult to establish exactly the cost saving on this but it should be taken note of.	Comment noted. The cost implications of managing side effects should be considered by the company in its submission, if appropriate. No changes to the scope

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			are needed.
	Novartis	None at this stage	Comment noted. No changes to the scope are needed.
Questions for consultation	British Association of Dermatologists	Yes, all relevant comparators have been included, although some patients with BRAF mutated metastatic melanoma will be treated with Ipilimumab first line. Outcomes listed are appropriate. It should be available as a first line combination therapy for patients with BRAF mutated melanoma, but could also be used second line after Ipilimumab or antiPD1.	Comment noted. Consultees considered that dabrafenib and vemurafenib are appropriate comparators for trametinib in combination with dabrafenib. The 'Other considerations' section has been amended to specify that, if evidence allows, consideration should be given to trametinib in combination with dabrafenib as a first-line therapy or after treatment with immunotherapy.
	Novartis	Novartis believes that questions for consultation were covered in previous discussions	Comment noted. No changes to the scope

Section	Consultee/ Commentator	Comments	Action
			are needed.
Additional comments on the draft scope	Novartis	n/a	Noted.

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 CLINICAL EXCELLENCE

Multiple/Single Technology Appraisal (MTA) (STA)

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

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.	Equalities National Council	Equalities National Council		Removed	This organisation's interests are not related to this appraisal topic Equalities National Council has been removed from the matrix of consultees and commentators under "patient groups"