NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vemurafenib for the adjuvant treatment of resected BRAF V600 mutation-positive melanoma with high risk of recurrence ID1250

Consultee and commentator comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional matrix of consultees and commentators. It is important that you complete and return this form even if you have no comments otherwise we may chase you for a response.

Enter the name of your organisation here: British Association of Dermatologists

Comments on the draft remit and draft scope

The draft remit is the brief for an appraisal. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the appraisal will answer.

Please submit your comments on the draft remit and draft scope using the table below. **Please take note of any questions that have been highlighted in the draft scope itself** (usually found at the end of the document).

If you have been asked to comment on documents for more than one appraisal, please use a separate comment form for each topic, even if the issues are similar.

Please complete this form and upload it to NICE Docs by **Tuesday 26 September 2017.** If using NICE Docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact the Scoping Project Manager, Michelle Adhemar on 44 (0)20 7045 2239 or at the email address above.

If you do not have any comments to make on the draft remit and draft scope, please state this in the box below.

Comment 1: the draft remit

Section	*Notes*	Your comments
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	Yes
Timing Issues	*What is the relative urgency of this appraisal to the NHS?*	Relatively urgent as this is a fast-moving field with significant advances being made.

Section	*Notes*	Your comments
Any additional comments on the draft remit No		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background information	*Consider the accuracy and completeness of this information.*	The background information looks accurate but does not take into consideration the other alternative adjuvant treatments available that have been published in recent trials. Also, single-agent vemurafenib is not generally standard of care for unresectable BRAF mutated metastatic melanoma as it has a significant associated toxicity, especially in skin with up to 75-80% of patients developing some sort of skin toxicity and nearly all patients remain photosensitive throughout treatment. Combination treatment such as with dabrafenib and trametinib has a lower skin toxicity profile. Sinha R et al. Br J Dermatol. 2015 Oct;173(4):1024-31. Cutaneous toxicities associated with vemurafenib therapy in 107 patients with BRAF V600E mutation-positive metastatic melanoma, including recognition and management of rare presentations.
The technology/ intervention	*Is the description of the technology or technologies accurate?*	Yes
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Yes
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	Current available adjuvant treatment in the NHS: interferon had been used as adjuvant therapy but is not standard of care due to poor tolerance and no overall survival advantage
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	Yes
Economic analysis	*Comments on aspects such as the appropriate time horizon.*	No additional comments
Equality	*NICE is committed to promoting*	No issues foreseen

Section	*Notes*	Your comments
	equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could 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;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*	
Other considerations	*Suggestions for additional issues to be covered by the appraisal are welcome.*	Recent evidence presented and published from ESMO and previously that discuss alternate adjuvant therapies in this setting need to be considered (see additional comments below)
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)?* *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?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	Where other innovative treatments that have better outcomes (see additional comments below) are not available then this may have a role.
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to*	

Section	*Notes*	Your comments
	result in changes to the planned time lines).	

Any additional comments on the draft scope:

There is no standard of care for the adjuvant treatment of stage III melanoma
Interferon is approved for this situation but improves relative relapse-free survival by just 20% compared to placebo.

Other recently reported trials on adjuvant therapies in melanoma are summarised below and would need to be taken into consideration if the scope allows.

Recent published trials:

1. Long G.V., Hauschild A., Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. DOI: 10.1056/NEJMoa1708539

COMBI-AD is a clinical trial of targeted therapies for adjuvant treatment of stage III melanoma. All patients had a BRAF mutation published this month in the NEJM. The primary endpoint of the trial was to prolong relapse-free survival.

This double-blind trial randomised 870 patients 1:1 to combination therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib versus matching placebos. Patients were treated for 12 months.

At a median follow-up of 2.8 years, the combination therapy had significantly reduced the risk of disease recurrence or death by 53% compared to placebo. The relapse-free survival benefit with the combination therapy was observed across all patient subgroups.
The combination treatment also showed a benefit in secondary endpoints including overall survival (HR, 0.57), distant metastases-free survival (HR, 0.51) and freedom from relapse (HR, 0.47).

Some 97% of patients on the combination had an adverse event of any kind and 41% had serious (grade 3/4) adverse events, compared to 88% and 14% with placebo, respectively. Around one-quarter (26%) of patients on the combination had to stop treatment due to adverse events versus 3% on placebo.

2. Alexander M.M. Eggermont, Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016; 375:1845-1855
Ipilimumab 10 mg/kg body weight

Adjuvant therapy for high-risk stage III melanoma, ipilimumab at a dose of 10 mg per kilogram resulted in significantly higher rates of recurrence-free survival, overall survival, and distant metastasis–free survival than placebo.

There were more immune-related adverse events with ipilimumab than with placebo. At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group
The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group.

The rate of distant metastasis-free survival at 5 years was 48.3% in the ipilimumab group, as compared with 38.9% in the placebo group. Adverse events of grade 3 or 4 occurred in 54.1% of the patients in the ipilimumab group and in 26.2% of those in the placebo group. Immune-related adverse events of grade 3 or 4 occurred in 41.6% of the patients in the ipilimumab group and in 2.7% of those in the placebo group. In the ipilimumab group, 5 patients (1.1%) died owing to immune-related adverse events

3. Jeffrey Weber Adjuvant nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. September 10, 2017DOI: 10.1056/NEJMoa1709030

Among patients undergoing resection of stage IIIB, IIIC, or IV melanoma, adjuvant

Section	*Notes*	Your comments
therapy with nivolumab resulted in significantly longer recurrence-free survival and a lower rate of grade 3 or 4 adverse events than adjuvant therapy with ipilimumab. At a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group. Treatment-related grade 3 or 4 adverse events were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any adverse event in 9.7% and 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment. 4. ESMO conference 2017.Abstract LBA7_PR 'BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected, BRAFV600+ melanoma at high risk for recurrence A randomised BRIM8 trial of adjuvant vemurafenib in patients with resected BRAF-mutant melanoma at high risk for recurrence. Adjuvant vemurafenib did not improve the primary endpoint of disease-free survival in patients with stage IIIC disease but appeared to be effective and well tolerated in patients with resected stage IIC–IIIB BRAF-mutant melanoma.		

Comment 3: provisional matrix of consultees and commentators

The provisional matrix of consultees and commentators (Appendix C) is a list of organisations that we have identified as being appropriate to participate in this appraisal. If you have any comments on this list, please submit them in the box below.

As NICE is committed to promoting equality and eliminating unlawful discrimination Please let us know if we have missed any important organisations from the lists contained within the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

If you do not have any comments to make on the provisional matrix of consultees and commentators, please cross this box: ☒

Comments on the provisional matrix of consultees and commentators

Comment 4: regulatory issues (to be completed by the company that markets the technology)

Section	*Notes*	Your comments
Remit	*Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.*	
Current or proposed marketing authorisation	*What are the current indications for the technology?*	
	What are the planned indications for the technology?	

Section	*Notes*	Your comments
	FOR EACH PLANNED INDICATION:	
	Which regulatory process are you following?	
	What is the target date (mm/yyyy) for regulatory submission?	
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)	
	What is the anticipated date (mm/yyyy) of regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK launch?	
	Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.	
Economic model software	*NICE accepts executable economic models using standard software, that is, Excel, DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non –standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software*	
Cancer Drugs Fund	*Please indicate whether this technology is likely to be a Cancer Drugs Fund candidate?*	

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