National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Novartis	The wording of the remit appropriately reflects the clinical and cost-effectiveness issues that the technology should consider.	Comment noted. No action required.
	British Association of Dermatologists	Yes	Comment noted. No action required.
Timing Issues	Novartis	The topic is highly appropriate given that treatments for melanoma in the adjuvant setting have not been previously assessed by NICE. This new approach to treatment may confer considerable benefits for patients. In addition, there is urgency for NICE to review this topic to ensure that patients receive access to effective medicines in an area where there is a clear unmet clinical need, with the intent of delaying/preventing progression to metastatic disease.	Comment noted. No action required.

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	British Association of Dermatologists	This is potentially a step change in adjuvant treatment for patients with melanoma at high risk of relapse and therefore should be considered as quickly as possible	Comment noted. No action required.
Additional comments on the draft remit	Novartis	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis	The background information states that a mutated form of the BRAF gene is found in approximately 50% of melanomas. We believe this figure to be an over-estimate, with more recent sources reporting a BRAF mutation rate of 40%.[1-6] [References provided but not reproduced here]	Comment noted. The estimate of 50% comes from a more recent estimate of BRAF+ prevalence in those with melanoma, than those found in references [1-5].
	British Association of Dermatologists	Generally covers the standard of care at present if patients are not entered into clinical trials however recent publications of other comparators such as Ipilumumab, Pembrolizumab, Nivolumab and Vemurafenib should be taken into account when looking at the possible adjuvant therapies in this patient group	Comment noted. No relevant comparators in the adjuvant setting have been identified. No change to the scope has been made.

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The technology/ intervention	Novartis	Please note a minor update to the technology description in bold below: From: *"Dabrafenib (Tafinlar, Novartis Pharmaceuticals) is a BRAF kinase inhibitor and trametinib (Mekinist, Novartis Pharmaceuticals) is inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2. Dabrafenib and trametinib are administered orally"* To: "Dabrafenib (Tafinlar, Novartis Pharmaceuticals) is a BRAF kinase inhibitor and trametinib (Mekinist, Novartis Pharmaceuticals) is **an** inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2. **Consequently, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and BRAF, with the combination of these therapies providing concomitant inhibition of the pathway.**[7,8] Dabrafenib and trametinib are administered orally" [References provided but not reproduced here]	Comment noted. The technology section of the scope has been updated accordingly.
	British Association of Dermatologists	Yes	Comment noted. No action required.
Population	Novartis	The population is currently defined as *"People with resected BRAF V600 positive malignant melanoma"* which is accurate; however, to be more specific and to reflect the population included in the key clinical trial for this indication (COMBI-AD),[9] we propose that the population be updated to: "People with **completely** resected, **stage III** melanoma with BRAF V600 positive **mutations**"	Comment noted. The population section of the scope has been updated accordingly.

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		The results of the COMBI-AD trial showed that the adjuvant use of dabrafenib plus trametinib in patients with stage III BRAF mutated melanoma resulted in a significantly lower risk of recurrence compared to the adjuvant use of placebo and was not associated with new toxic effects. This clinical benefit of dabrafenib and trametinib combination therapy was consistent across all subgroups of patients in the analysis, regardless of lymph-node involvement or primary tumour ulceration and as such, it is not intended for any subgroups to be considered separately.[9] [References provided but not reproduced here]	
	British Association of Dermatologists	Only patients with BRAF mutated melanoma can be considered for this adjuvant therapy	Comment noted. No action required.
Comparators	Novartis	Routine surveillance is the standard of care in this patient population in the UK. Although interferon alpha-2b is the only systemic adjuvant therapy licensed in the UK, current UK guidelines do not recommend its use due to the uncertainty of its clinical effectiveness and the burden of associated side effects.[10] [References provided but not reproduced here]	Comment noted. No action required.
	British Association of Dermatologists	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	Comment noted. No relevant comparators in the adjuvant setting have been identified. No action required.

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Outcomes	Novartis	The outcome measures should reflect those assessed in the key trial (COMBI-AD)[9] for the intervention being appraised. As such, the primary and secondary outcomes are as follows: Primary Outcomes • **Relapse-free survival** Defined as the time from randomisation to disease recurrence or death from any cause Secondary Outcomes • **Overall survival** Defined as the interval from randomisation to the date of death, irrespective of the cause of death • **Distant metastases-free survival** Defined as the time from randomisation to the date of first distant metastasis or date of death, whichever occurred first • **Freedom from relapse** Defined as the time from randomisation to recurrence, with censoring of data for patients who had died from causes other than melanoma or treatment-related toxic effects • **Adverse effects of treatment** • **Health-related quality of life**	Comment noted. The scope has been updated accordingly.

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	British Association of Dermatologists	Yes	Comment noted. No action required.
Economic analysis	Novartis	The economic analysis is appropriate and consistent with the NICE reference case.	Comment noted. No action required.
	British Association of Dermatologists	No additional comments	Comment noted. No action required.
Equality and Diversity	Novartis	No comment.	Comment noted. No action required.
	British Association of Dermatologists	No issues with equality	Comment noted. No action required.
Innovation	Novartis	Surgical resection is the standard treatment for early-stage melanoma, and is associated with an excellent long-term prognosis (five-year survival rates of approximately 100% for stage I disease and 78-85% for stage II disease).[11] However, patients with stage III melanoma have a poorer long-term prognosis with five-year survival rates of 50-55%.[11] These patients are also more likely to experience disease recurrence, with a 10-year recurrence-free survival of only 36%.[12] Therefore there is a growing need for effective, therapies that significantly improve recurrence-free survival and overall survival. Although interferon alpha-2b is licensed for adjuvant melanoma in the UK, it has shown inconsistent improvements in overall survival and is associated	Comment noted. The committee will consider the innovative nature of dabrafenib in combination with trametinib in terms of a step-change in clinical effectiveness or a novel method of action.

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		with substantial toxicities.[13-15] Dabrafenib in combination with trametinib subsequently represents an innovative step-change in the management of melanoma in the adjuvant setting, by offering a clinically effective treatment for patients with a known and manageable safety profile.[9] Dabrafenib in combination with trametinib is the first targeted combination therapy to show a significantly lower risk of recurrence compared to the adjuvant use of placebo in stage III melanoma. This targeted combination therapy provides concomitant inhibition of the MAPK pathway by simultaneously targeting two discrete kinases, overcoming the limitations associated with resistance to BRAF inhibitor monotherapy.[7, 8] [References provided but not reproduced here]	
	British Association of Dermatologists	The recent published data in the New England medical journal on this technology by Long et al do suggest a significant benefit for this treatment in the adjuvant setting given over a year: Summarised as follows: 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. 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.	Comment noted. The committee will consider all clinical evidence which is presented to them, to make a decision on the innovative nature of the interventions.

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		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). Toxicity should be considered by this appraisal committee as 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.	
Other considerations	Novartis	No comment.	Comment noted. No action required.
Questions for consultation	Novartis	**Are there any adjuvant treatments for resected V600 mutation-positive malignant melanoma? If yes, could any of these treatments be considered as a relevant comparator to dabrafenib in combination with trametinib?** The only licensed therapy for the adjuvant treatment of resected V600 mutation-positive malignant melanoma in the UK is interferon alpha-2b; however, current UK guidelines do not recommend its use due to the uncertainty of its clinical effectiveness and the burden of associated side effects[10] and as such, routine surveillance represents the only relevant comparator in the context of this appraisal. **Is dabrafenib in combination with trametinib intended to be used in people with high risk of recurrence? How is high risk recurrence defined?** Dabrafenib in combination with trametinib is intended to be used in all people with stage III melanoma, all of whom are at high risk of disease recurrence.[12]	Comment noted. No change to the scope is required. Comment noted. No action required.

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		Recent data from the COMBI-AD trial demonstrated that the adjuvant use of dabrafenib in combination with trametinib resulted in a significantly lower risk of recurrence in patients with BRAF-positive stage III disease than placebo (hazard ratio for relapse or death, 0.47; 95% CI, 0.39 to 0.58; P<0.001).[9] This statistically significant and clinically meaningful survival benefit of combination therapy was consistently observed across all subgroups of stage III disease[16] (see Table 1 below), highlighting the need for clinically effective and tolerable therapies in these patients. **Table 1 not reproduced here** **Are the outcomes listed appropriate?** The outcomes listed in the scope are appropriate and reflect the endpoints assessed in the COMBI-AD trial; however, as discussed in our previous comments on outcomes, freedom from relapse (a secondary endpoint in the COMB-AD trial), should also be included. **Are there any subgroups of people in whom dabrafenib in combination with trametinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** There are no known subgroups of people in whom dabrafenib in combination with trametinib is expected to be more clinically effective or cost effective, since a consistent clinical benefit of a significantly lower risk of recurrence was observed across all subgroups with dabrafenib and trametinib combination therapy compared to placebo.[9] **Where do you consider dabrafenib in combination with trametinib will fit into the existing NICE pathway, Melanoma?** The existing NICE pathway for melanoma relates to unresectable and advanced or metastatic disease, and does not currently consider resected disease and systemic adjuvant therapy.[17]	

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		As a consequence of the multiple therapies currently in clinical development for the adjuvant treatment of resected melanoma, we acknowledge that the NICE pathway for melanoma will need to be updated to reflect the future landscape of adjuvant therapies.	Comment noted. No action required.
		NICE is committed to promoting 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 dabrafenib in combination with trametinib 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.**	Comment noted. No action required. Comment noted.
		Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. No comment.	
		Do you consider dabrafenib in combination with trametinib 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	

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		need is met (is this a 'step-change' in the management of the condition)? Dabrafenib in combination with trametinib represents a step-change in the management of patients with stage III melanoma. Currently, patients receive no systemic therapy adjunctive to surgery and have often been entered into clinical trials.[18] Consequently, dabrafenib in combination with trametinib is the first and only targeted therapy to demonstrate a statistically significant improvement in relapse-free survival in patients with BRAF-mutated melanoma, with an estimated three-year relapse-free survival rate of 58% compared to 39% in the placebo group (P<0.001).[9] Combination therapy also resulted in higher rates of overall survival, with an estimated three-year overall survival rate of 86% compared to 77% in the placebo group (P=0.0006).[9] In addition, the majority of patients on combination therapy in COMBI-AD completed the scheduled 12 months of therapy with a median dose close to the scheduled dose for each drug, and the safety profile of the combination therapy was consistent with the known profile of these therapies.[9] **Do you consider that the use of dabrafenib in combination with trametinib 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.** No comment. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**	Comment noted. No action required. Comment noted. The committee will consider the innovative nature of dabrafenib in

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		There are not expected to be any barriers to the adoption of dabrafenib and trametinib in the adjuvant setting in clinical practice. [References provided but not reproduced here]	combination with trametinib in terms of a step-change in clinical effectiveness or a novel method of action. Comment noted. No action required. Comment noted. No action required.
	Novartis	None	Comment noted. No action required.

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Additional comments on the draft scope	British Association of Dermatologists	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. 1.Ipilumumab significant benefit but with significant toxicity 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	Comment noted. No action required.

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		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 2. Nivolumab also shows significant benefit and it should be noted that this trial comapres Nivolumab to Ipilumumab not placebo. Less significant toxicity in the Nivolumab group needs to be considered as beneficial Jeffrey Weber Adjuvant nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. September 10, 2017 DOI: 10.1056/NEJMoa1709030 Among patients undergoing resection of stage IIIB, IIIC, or IV melanoma, adjuvant 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. 3.. Single agent Vemurafenib has also been reported as adjuvant therapy for patients with melanoma at high risk 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	

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		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.	

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

None