NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dabrafenib and trametinib for the treatment of unresectable, advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of dabrafenib and trametinib within their licensed indications for the treatment of unresectable, advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma.

Background

Malignant melanoma is a type of skin cancer which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable by resection. However, at presentation, around 10% of malignant melanomas will have metastasised. Melanoma can spread to nearby lymph nodes (stage III, of which stage IIIc disease includes tumours of varying size with extensive lymph node involvement but no metastases) or to other parts of the body (stage IV). It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at greatly increased risk.

The incidence of malignant melanoma is increasing in England and Wales with rates doubling approximately every 10-20 years. There were 11,877 new diagnoses of malignant melanoma and 2203 deaths registered in the UK in 2010. In the UK, melanoma is diagnosed at a mean age of around 50 years but approximately 20% of cases occur in young adults aged between 15 and 39 years old. Five-year survival rates are approximately 20-30% for stage IIIc disease and approximately 7-20% for stage IV disease.

BRAF is part of the RAS/MAPK signalling pathway, which helps to control cell proliferation, differentiation and death. Companion diagnostic tests can be used to detect the BRAF mutation, including the cobas test, generic PCR sequencing tests and other validated BRAF mutation tests. The mutated form $BRAF^{V600}$ is found in approximately 50% of malignant melanomas.

Early recognition of malignant melanoma and accurate diagnosis presents the best opportunity for cure by surgical resection of the tumour. A very small minority of people with advanced disease can still have their tumour removed. People with unresectable stage III or IV (metastatic) disease are usually managed by a specialist oncologist and first-line standard care normally involves the administration of dacarbazine. Radiotherapy, immunotherapy and combination chemotherapy have also been studied in randomised clinical trials. NICE technology appraisal No. 269 recommends vemurafenib as an option for treating $BRAF^{V600}$ mutation-positive unresectable or metastatic

melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme. NICE technology appraisal No. 268 recommends ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. A NICE technology appraisal of ipilimumab for previously untreated unresectable stage III or IV malignant melanoma is currently ongoing.

The technology

Dabrafenib (Tafinlar, GlaxoSmithKline) is a selective ATP-competitive BRAF (serine/threonine-protein kinase BRAF) inhibitor. When the activity of mutant protein kinase is blocked, the cancer cells stop growing and die. It is administered orally.

Dabrafenib does not currently have a UK marketing authorisation for the treatment of metastatic melanoma. The Committee for Medicinal Products for Human Use has adopted a positive opinion, recommending the granting of a marketing authorisation for dabrafenib for the treatment of adults with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.

Trametinib (Brand name unknown, GlaxoSmithKline) is a down-regulator of MEK 1 and 2 which are key components of the mitogen-activated protein kinase (MEK) signalling pathway that regulates cell growth. In BRAF mutant melanoma, MEK activation is a driver of the disease. Trametinib binds to MEK 1 and 2, thereby inhibiting cellular signalling and growth. It is administered orally.

Trametinib does not currently have a UK marketing authorisation for the treatment of metastatic melanoma. Trametinib alone has been studied in clinical trials compared with dacarbazine or paclitaxel in adults with unresectable or metastatic stage IIIc or IV $BRAF^{V600}$ mutation-positive cutaneous melanoma who have not received more than one prior chemotherapy regimen.

Trametinib and dabrafenib combination therapy has also been studied in clinical trials compared with dabrafenib alone and compared with vemurafenib in adults with unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma who have not received prior systemic chemotherapy.

Intervention(s)	• Combination therapy with dabrafenib and trametinib • Dabrafenib monotherapy • Trametinib monotherapy
Population(s)	People with advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma

Comparators	Combination therapy will be compared with both monotherapies For people with previously untreated malignant melanoma: • dacarbazine • vemurafenib For people with previously treated malignant melanoma: • dacarbazine • ipilimumab • vemurafenib For people whose malignant melanoma has metastasised to the brain: • radiotherapy
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Cost of any additional mutational testing required for

	this treatment should be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 268, December 2012, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. Review decision date November 2014. Technology Appraisal No.269, December 2012, 'Vemurafenib for treating locally advanced or metastatic BRAF^{V600} mutation-positive malignant melanoma'. Review decision date November 2014. Technology Appraisal in Preparation, 'Ipilimumab for previously untreated unresectable malignant melanoma'. Earliest anticipated date of publication June 2014. Other Guidance: Cancer Service Guidance, May 2010, 'Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community'

Questions for consultation

Have the most appropriate comparators for dabrafenib monotherapy, trametinib monotherapy and dabrafenib/trametinib combination therapy for the treatment of unresectable, advanced or metastatic BRAF^{V600} mutation-positive melanoma been included in the scope?

Are BRAF inhibitors likely to be used in sequence? If so, where in the sequence would dabrafenib and trametinib (alone and in combination) most likely be used?

Are the comparators listed routinely used in clinical practice? Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

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 and 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 technologies;
- 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.

Do you consider dabrafenib and trametinib to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (are these treatments a 'step-change' in the management of the condition)?

Do you consider that the use of dabrafenib and 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.