NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

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

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of cobimetinib in combination with vemurafenib within its marketing authorisation for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

Background

Melanoma is a cancer of the skin which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable. Melanoma can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). At presentation, around 1% of melanomas are in stage IV. It occurs more commonly in fair-skinned people and there is strong evidence that it is caused by ultra violet exposure. 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 with rates doubling approximately every 10-20 years. There were 11,121 new diagnoses of malignant melanoma in England in 2011. In 2012, there were 1,781 deaths from malignant melanoma of the skin in England. In the UK, melanoma is diagnosed at a mean age of around 50 years but approximately 13% of diagnoses are in young adults aged between 15 and 39 years old.

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. The mutated form BRAF V600 is found in approximately 50% of melanomas.

Early recognition of 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 at presentation can still have their tumours removed. Metastatic melanoma can be treated with biological therapy, chemotherapy, radiotherapy or surgery. People whose disease presents with a BRAF gene mutation will receive targeted therapy. NICE technology appraisals No. 269 and 321 recommend vemurafenib or dabrafenib respectively as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the companies provide them with the discount agreed in the patient access scheme. NICE technology appraisals No. 319 and 268 recommend ipilimumab for untreated or previously treated unresectable stage III or IV malignant melanoma only if the

company provides them with the discount agreed in the patient access scheme.

The technology

Cobimetinib (brand unknown, Roche Products) inhibits the MEK component of the mitogen-activated protein kinases signalling pathway. MEK inhibitors given in combination with BRAF inhibitors may delay the emergence of acquired drug resistance in tumour cells. Cobimetinib is administered orally.

Cobimetinib in combination with vemurafenib does not currently have a marketing authorisation in the UK for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. It has been studied in a clinical trial in combination with vemurafenib, compared with vemurafenib alone in adults with unresectable stage IIIc or stage IV metastatic melanoma who had not received any previous treatment.

Intervention(s)	Cobimetinib in combination with vemurafenib
Population(s)	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.
Comparators	• dabrafenib • vemurafenib
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 comparator technologies should be taken into account. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No.321, Oct 2014, 'Dabrafenib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma' Review Proposal Date October 2017. Technology Appraisal No.319, July 2014, 'Ipilimumab for previously untreated (unresectable or advanced) malignant melanoma' Review Proposal Date June 2017. Technology Appraisal No.268, Dec 2012, 'Ipilimumab for previously treated unresectable stage III or IV malignant melanoma' Review Proposal Date November 2014. Technology Appraisal No.269, Dec 2012, 'Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation positive malignant melanoma' Review Proposal Date November 2014. Proposed technology appraisal, 'Pembrolizumab for treating advanced melanoma'. Batch 38. Publication TBC. Related Guidelines: Clinical Guideline in Preparation, 'Melanoma:

	assessment and management of melanoma' Earliest anticipated date of publication July 2015. Related Pathways: Skin cancer overview: Melanoma, Pathway created March 2014 http://pathways.nice.org.uk/pathways/skin-cancer#content=view-node%3Anodes-melanoma Other guidance: Cancer Service Guidance CSGSTIM, May 2010, 'Improving outcomes for people with skin tumours including melanoma'.
Related National Policy	Department of Health, 2011, 'Improving outcomes: a strategy for cancer' Department of Health, 2009, 'Cancer commissioning guidance' Department of Health, NHS Outcomes Framework 2013-2014, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Have all relevant comparators for cobimetinib been included in the scope? Are ipilimumab or dacarbazine appropriate comparators for this patient population?

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

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?

Where do you consider cobimetinib will fit into the existing NICE pathway, for skin cancer?

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 cobimetinib 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.

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)?

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?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction