NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Draft scope

Draft remit/appraisal objective

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

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Most melanomas occur in people with pale skin. The risk factors are skin that tends to burn in the sun, having many moles, sun exposure and sunburn.

There were 12,993 new diagnoses of melanoma and 2,080 deaths registered in England in 2014.[2] In England in 2012-2013, 9% of cases were diagnosed at stage III or IV.[2] In the UK in 2012-2014, approximately half of new diagnoses were in people aged 65 and over[2].

A mutated form of the BRAF gene is found in about 50% of melanomas; over 90% of these are BRAF V600 mutations.[3] Mutated BRAF genes activate the RAF-MEK-ERK pathway, leading to uncontrolled cell division and growth of the tumour.

Treatment options for advanced melanoma depend on the person's BRAF mutation status and treatment history. In clinical practice, for people with BRAF mutation-positive advanced melanoma, a BRAF inhibitor is the usual first-line treatment. For BRAF V600 mutation-positive unresectable or metastatic melanoma, NICE technology appraisal guidance recommends the BRAF inhibitor, dabrafenib alone (TA321) or in combination with the MEK inhibitor, trametinib (TA396) and the BRAF inhibitor, vemurafenib alone (TA269). NICE technology appraisal guidance 414 does not recommend the use of vemurafenib in combination with the MEK inhibitor, cobimetinib for treating BRAF V600 mutation-positive advanced melanoma. Immunotherapy is also recommended for advanced melanoma.

The technology

Encorafenib and binimetinib (brands unknown, Array BioPharma Inc and Pierre Fabre) inhibit the actions of the BRAF V600 gene and MAP kinase 1

and 2 (MEK1/2) respectively, with the aim of slowing the growth and spread of the cancer. Encorafenib and binimetinib are administered orally.

Encorafenib in combination with binimetinib 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 compared with encorafenib or vemurafenib alone, in adults with advanced BRAF V600 mutation-positive melanoma.

Intervention(s)	Encorafenib in combination with binimetinib
Population(s)	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma
Comparators	Trametinib in combination with dabrafenib
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 will be taken into account.

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: 'Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma' (2016). NICE Technology Appraisal 414. Review date October 2019. 'Talimogene laherparepvec for treating unresectable metastatic melanoma' (2016). NICE Technology Appraisal 410. Review date September 2019. 'Nivolumab in combination with ipilimumab for treating advanced melanoma' (2016). NICE Technology Appraisal 400. Review date July 2019. 'Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma' (2016). NICE Technology Appraisal 396. Review date June 2019. 'Nivolumab for treating advanced (unresectable or metastatic) melanoma' (2016). NICE Technology Appraisal 384. Review date February 2019. 'Pembrolizumab for advanced melanoma not previously treated with ipilimumab' (2015). NICE Technology Appraisal 366. Review date November 2018. 'Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab' (2015). NICE Technology Appraisal 357. Review date October 2018. 'Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma' (2014). NICE Technology Appraisal 321. Review date October 2017. 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma' (2014). NICE Technology Appraisal 319. Review date to be confirmed. 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma' (2012). NICE Technology Appraisal 269. Static list. 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma' (2012). NICE Technology Appraisal 268. Static list. Appraisals in development (including suspended

	appraisals) 'Vemurafenib for treating BRAF V600 mutation-positive metastatic melanoma in people under 18 years' NICE technology appraisals guidance [ID956]. Publication date to be confirmed. Related Guidelines: 'Melanoma: assessment and management' (2015) NICE guideline NG14. Review date to be confirmed. 'Improving outcomes for people with skin tumours including melanoma' (2006) NICE Cancer Service guideline CSG8. Review date March 2018. Related Quality Standards: 'Skin cancer' (2016) NICE quality standard 130. Related NICE Pathways: Melanoma (2016) NICE pathway.
Related National Policy	Department of Health Cancer research and treatment Department of Health (2016) NHS outcomes framework 2016 to 2017: Domains 1–5. Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2016) Manual for Prescribed Specialised Services 2016/17. Chapter 105. Specialist cancer services (adults). NHS England (2013) NHS standard contract for cancer: skin (adult) A12/S/b.

Questions for consultation

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

Is BRAF inhibitor monotherapy used in clinical practice in this population? If yes, is BRAF inhibitor monotherapy an appropriate comparator for combination therapy with encorafenib and binimetinib?

Have all relevant comparators for encorafenib in combination with binimetinib been included in the scope?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom encorafenib in combination with binimetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider encorafenib in combination with binimetinib will fit into the existing NICE pathway, Melanoma?

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 encorafenib in combination with binimetinib 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 encorafenib in combination with binimetinib 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 encorafenib in combination with binimetinib 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.

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.

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).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Armstrong BK, Cust AE. (2017) Sun exposure and skin cancer, and the puzzle of cutaneous melanoma: a perspective on Fears et al. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. Cancer Epidemiology 48: 147-156.

2. Cancer Research UK (2014) Skin cancer statistics. Accessed August 2017.

3. Ascierto PA, Kirkwood JM, Grob J-J, et al. (2012) The role of BRAF V600 mutation in melanoma. Journal of Translational Medicine 10:85.