NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Binimetinib for treating advanced, unresectable or metastatic NRAS mutation positive melanoma

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of binimetinib within its marketing authorisation for treating advanced, unresectable or metastatic NRAS 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, intermittent sun exposure and sunburn.

There were 11,281 new diagnoses of melanoma[1] and 1781 deaths registered in England in 2012.[2] In the UK, about 27% of people diagnosed with melanoma are younger than 50 years.[3] At diagnosis, around 1% of melanomas are stage IV.[3]

The NRAS mutation is found in approximately 15-25% of melanomas.[4] NRAS mutation positive-melanoma is usually associated with a rapidly progressing disease. NRAS mutations are not commonly found in tumours with BRAF mutations.

There are currently no targeted treatment options available for people with unresectable or metastatic NRAS mutation-positive melanoma. Treatment options involve immunotherapy or chemotherapy. NICE TA guidance 319 and 268 recommend ipilimumab, for untreated or previously treated advanced (unresectable or metastatic) melanoma. Pembrolizumab is also recommended for treating advanced melanoma before or after disease progression with ipilimumab (NICE TA guidance 366 and 357). NICE clinical guideline CG14 recommends dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy is not suitable.

The technology

Binimetinib (brand name unknown, Pierre Fabre) is a MEK inhibitor which inhibits the signalling pathway in tumour cells with the aim of slowing the growth and spread of the cancer. Binimetinib is administered orally.

Binimetinib does not currently have a marketing authorisation in the UK for treating advanced, unresectable or metastatic NRAS mutation-positive melanoma. It has been studied in a clinical trial compared with dacarbazine alone in adults with unresectable stage IIIc or stage IV metastatic melanoma who had not received any previous treatment with a MEK inhibitor.

Intervention(s)	Binimetinib
Population(s)	People with advanced, unresectable or metastatic NRAS mutation-positive melanoma.
Comparators	• Dacarbazine • Ipilimumab • Pembrolizumab • Best supportive care
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.

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. The use of binimetinib is conditional on the presence of the NRAS mutation. The economic modelling should include the costs associated with diagnostic testing for the NRAS mutation in people with advanced, unresectable or metastatic melanoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (2014). NICE Technology Appraisal 319. Review date June 2017. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (2012). NICE Technology Appraisal 268. Moved to static list, April 2015. Pembrolizumab for treating advanced melanoma after disease progression with Ipilimumab (2015). NICE Technology Appraisal 357. Review date October 2018. **Appraisals in development (including suspended appraisals)** Pembrolizumab for treating melanoma (unresectable, metastatic, ipilimumab naive). NICE technology appraisals guidance [ID801]. Publication expected November 2015. Nivolumab (with ipilimumab) for treating melanoma (untreated, advanced, unresectable, metastatic) [ID848]. Publication expected September 2016. Ipilimumab (adjuvant) for treating Melanoma (resected stage IV, high risk stage III). [ID721]. Publication to be confirmed. Talimogene laherparepvec for treating metastatic melanoma. [ID508]. Publication to be confirmed. Paclitaxel (as albumin-bound nanoparticles) for the first-line treatment of metastatic melanoma. [ID570].

	Suspended. Temozolomide for the treatment of advanced and metastatic melanoma. [ID316]. Suspended. **Related Guidelines:** Melanoma: assessment and management of melanoma (2015). NICE guideline 14. Review date to be confirmed. **Related Quality Standard:** In development: skin cancer. NICE quality standard. Publication expected August 2016. **Related NICE Pathway:** Skin cancer (updated February 2015) NICE pathway. http://pathways.nice.org.uk/pathways/skin-cancer **Other guidance:** Cancer Service Guidance, 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. NHS England Manual for Prescribed Specialised Services 2013/14. Chapter 105. Specialist cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Are people with advanced melanoma commonly tested for the presence of the NRAS mutation?

Have all relevant comparators for binimetinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for people with advanced, unresectable or metastatic NRAS mutation positive melanoma?

Do some people with NRAS mutations also have BRAF mutations? If so should BRAF inhibitors be included as a comparator?

Are the outcomes listed appropriate?

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

Where do you consider binimetinib will fit into the existing NICE pathway, http://pathways.nice.org.uk/pathways/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 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 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 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.

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)

References

1. Office for National Statistics (2014) Cancer Statistics Registrations, England 2012. Accessed July 2015.

2. Cancer Research UK (2015) Skin cancer mortality statistics. Accessed July 2015.

3. Cancer Research UK (2015) Skin cancer incidence statistics. Accessed July 2015.

4. Lee JH, Choi JW and Kim YS. Frequencies of BRAF and NRAS mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. The British Journal of Dermatology 2011;164(4):776-784.