NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of dabrafenib and trametinib within their licensed indications 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, 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 3% of melanomas are stage IV.[3]

A mutated form of the BRAF gene (called BRAF V600) is found in about 50% of melanomas. The mutated gene means that the cells produce too much BRAF protein, leading to uncontrolled cell division and growth of the tumour.

Treatment options for advanced (unresectable or metastatic) melanoma depend on the person's BRAF mutation status and their treatment history. NICE technology appraisals (TA) guidance 269 and 321 recommend the BRAF inhibitors vemurafenib or dabrafenib respectively as options for treating BRAF V600 mutation-positive unresectable or metastatic melanoma. NICE TA guidance 319 and 268 recommend ipilimumab, which is not a BRAF-targeted therapy, for untreated or previously treated advanced (unresectable or metastatic) melanoma. In clinical practice, for people with BRAF mutation-positive advanced melanoma, a BRAF inhibitor is the usual first-line treatment; ipilimumab may be considered for first-line use in a subgroup of patients who are relatively well and in whom the disease is not progressing rapidly.

The technology

Trametinib (Mekinist, Novartis Pharmaceuticals) is an inhibitor of MEK1 and MEK2 kinases. Trametinib inhibits the action of the abnormal BRAF protein, with the aim of slowing the growth and spread of the cancer.

Trametinib and dabrafenib have marketing authorisations in the UK, as monotherapies or in combination with each other, for treating adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Both trametinib and dabrafenib are administered orally.

Intervention(s)	Trametinib in combination with dabrafenib
Population	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 the intervention or comparator technologies will be taken into account.
Other considerations	If evidence allows, consideration should be given to trametinib in combination with dabrafenib as a first-line therapy or after treatment with immunotherapy. 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: Dabrafenib for treating unresectable or metastatic BRAFV600 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 June 2017. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (2012). NICE Technology Appraisal 268. Moved to static list, April 2015. Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation positive malignant melanoma (2012). NICE Technology Appraisal 269. Moved to static list, January 2015. Appraisals in development Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab. NICE technology appraisals guidance [ID760]. Publication expected October 2015. Pembrolizumab for treating ipilimumab naive unresectable, metastatic melanoma. NICE technology appraisals guidance [ID801]. Publication expected November 2015. Nivolumab for treating advanced, unresectable or metastatic melanoma. NICE technology appraisals guidance [ID845]. Publication expected May 2016. Cobimetinib with vemurafenib for treating advanced, unresectable or metastatic BRAF V600 mutation-positive melanoma. NICE technology appraisals guidance [ID815]. Publication expected June 2016. Talimogene laherparepvec for treating metastatic melanoma. NICE technology appraisals guidance [ID508]. Publication expected July 2016. 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 2015–2016, Dec 2014. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

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

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

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