NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of vemurafenib within its licensed indication for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma.

Background

Cutaneous melanoma is a malignant tumour of the skin which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable. However, at presentation, 10% of cutaneous melanomas will have metastasised. Melanoma can spread to nearby lymph nodes (stage III, of which stage IIIc disease includes tumours of varying size with lymph node involvement [large enough to be visible on imaging tests or clinically palpable], 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 10297 new diagnoses of malignant melanoma and 1847 deaths registered in England and Wales in 2008. 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.

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. The treatment options for second or subsequent line therapy are limited

The technology

Vemurafenib (brand unknown, Roche Products) is administered orally and inhibits the oncogenic BRAFV600 protein kinase. BRAF is part of the RAS/MAPK signalling pathway, which helps to control the proliferation, differentiation and apoptosis of cells. The mutated isoform, BRAFV600, is found in approximately 50% of malignant melanomas.

Vemurafenib does not have a UK marketing authorisation for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma. It has been studied as monotherapy in clinical trials in previously untreated adults with stage IIIc or IV BRAFV600 mutation-positive melanoma compared with dacarbazine, and in single arm trials in adults with clinical evidence of disease progression during or after at least one prior systemic therapy.

Intervention(s)	Vemurafenib
Population(s)	People with unresectable locally advanced or metastatic BRAFV600 mutation-positive malignant melanoma
Comparators	For people with previously untreated malignant melanoma: • Dacarbazine For people with previously treated malignant melanoma: • Ipilimumab (subject to ongoing NICE appraisal) Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression free 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. Costs of any additional mutational testing required for this treatment should be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal in Preparation, 'Ipilimumab for previously treated unresectable stage III or IV malignant melanoma'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Temozolomide for advanced and metastatic melanoma' Suspended. Proposed Technology Appraisal, 'OncoVEX GM-CSF for the treatment of unresectable stage IIIc or IV metastatic melanoma. Earliest anticipated date of publication TBC.