NICE National Institute for Health and Care Excellence

NICE guidance

Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Encorafenib with binimetinib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma in adults. It is recommended only if the company provides encorafenib and binimetinib according to the commercial arrangements.

Why the committee made these recommendations

Current treatments for unresectable or metastatic BRAF V600 mutation-positive melanoma include targeted therapy, usually using a combination of a BRAF and MEK inhibitor (dabrafenib with trametinib) or sometimes monotherapy with a BRAF inhibitor (vemurafenib or dabrafenib).

Clinical trial evidence shows that, compared with vemurafenib, encorafenib with binimetinib extends the time until melanoma progresses and also how long people live. There are no trials directly comparing it against dabrafenib with trametinib. But compared indirectly, encorafenib with binimetinib appears to be as effective as dabrafenib with trametinib.

When the commercial arrangements for encorafenib, binimetinib, dabrafenib and trametinib are taken into account, encorafenib with binimetinib is considered to be a cost-effective use of NHS resources. It is therefore recommended.

2 Information about encorafenib with binimetinib

Marketing authorisation

2.1 Encorafenib (Braftovi, Pierre Fabre) in combination with binimetinib (Mektovi, Pierre Fabre) is indicated for 'the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation'.

Dosage in the marketing authorisation

2.2 For encorafenib, the recommended dose is 450 mg (6×75-mg capsules) taken orally, once daily. For binimetinib, the recommended dose is 45 mg (3×15-mg tablets) taken orally, twice daily, 12 hours apart.

Price

2.3 The list price for 42 capsules of encorafenib 75 mg is £1,400 and for 84 tablets of binimetinib 15 mg is £2,240 (company submission). The company has a commercial arrangement for each drug. This makes encorafenib with binimetinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Pierre Fabre and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical need and current management

People with unresectable or metastatic BRAF V600 mutation-positive melanoma would welcome an additional treatment option

3.1 Melanoma often affects people at a younger age than some other cancers. It has a substantial effect on patients, their carers and wider society. Advanced (unresectable or metastatic) melanoma can cause severe and debilitating symptoms and is life threatening. The clinical and patient experts stated that they would welcome the availability of another targeted combination treatment for BRAF V600 mutation-positive melanoma, in addition to the currently available combination of dabrafenib with trametinib. Encorafenib with binimetinib has a different toxicity profile. The patient expert emphasised the value of having a choice of treatments available and that a favourable safety profile would improve the quality of life of patients. The committee concluded that people with unresectable or metastatic BRAF V600 mutation-positive melanoma would welcome an additional treatment option.

The position in the care pathway is uncertain for targeted therapies of BRAF V600 mutation-positive melanoma

3.2 The committee acknowledged that the management of unresectable or metastatic BRAF V600 mutation-positive melanoma is changing rapidly with the availability of new immunotherapy and other treatments. The clinical experts explained that standard treatment is either immunotherapies such as nivolumab, ipilimumab or pembrolizumab (alone or in combination) or targeted therapy.

Targeted therapy is usually dabrafenib in combination with trametinib but sometimes dabrafenib, trametinib or vemurafenib are taken alone. The clinical experts explained that there is no consensus on whether first-line treatment should be targeted therapies or immunotherapies. They noted that there may be a preference to use immunotherapies first-line for people who have a good performance status, however this is not standard practice across the NHS. Most patients with BRAF V600 mutation-positive melanoma are likely be offered a targeted therapy at some point in the treatment pathway. The committee concluded that the management of advanced melanoma is evolving, making it difficult to determine the position of targeted therapies in the care pathway for mutation-positive melanoma.

Clinical evidence

The clinical evidence is relevant to clinical practice in England but does not provide a direct comparison with the comparator specified in the scope

3.3 The clinical evidence comes from COLUMBUS. This is an open-label, randomised trial of encorafenib plus binimetinib compared with vemurafenib in people with unresectable or metastatic BRAF V600 mutation-positive melanoma. It included people who had not had treatment for advanced disease, and people with disease that had progressed on or after first-line immunotherapy. The ERG explained that very few people in COLUMBUS had brain metastases, and that people with a poor performance status (2 or above) were excluded from the trial. However, the clinical experts noted that people with unresectable or metastatic BRAF V600 mutation-positive melanoma generally have good performance status even with high-volume disease. The ERG highlighted that only 6% of people in the trial had had treatment with immunotherapy for metastatic disease, which may not reflect the population in the NHS who would have encorafenib and binimetinib. The committee recalled that there is no consensus on whether immunotherapies or targeted therapy should be used first in advanced mutation-positive melanoma (see section 3.2). It noted that the clinical experts do not consider that immunotherapy will affect the response to subsequent targeted therapies, because of their different mechanism of action. The ERG noted that

although COLUMBUS has some limitations, overall it was well conducted and generally representative of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma who would be treated in the NHS. The committee concluded that COLUMBUS was well conducted and representative of clinical practice in England but noted that it does not directly compare encorafenib with binimetinib against dabrafenib with trametinib, which is the comparator specified in the NICE scope.

Encorafenib with binimetinib is more clinically effective than vemurafenib in the clinical trial population

3.4 Progression-free survival, assessed by blinded independent review, is the primary endpoint in COLUMBUS. At a median follow up of 11.8 months, median progression-free survival for encorafenib with binimetinib is 14.9 months (95% confidence interval [CI] 11.0 to 18.5) compared with 7.3 months (95% CI 5.6 to 8.2) for vemurafenib. The committee noted that the hazard ratio (HR) for progression-free survival for encorafenib with binimetinib compared with vemurafenib is 0.54 (95% CI 0.41 to 0.71), representing an estimated 46% reduction in the risk of disease progression. It also noted that investigator-assessed progression-free survival is very similar to the results from blinded independent review. In addition, median overall survival is longer for encorafenib with binimetinib (33.6 months; 95% CI 24.4 to 39.2) compared with vemurafenib (16.9 months; 95% CI 14.0 to 24.5), representing a 39% reduction in the risk of death (HR 0.61, 95% CI 0.47 to 0.79; $p<0.0001$). The committee concluded that encorafenib with binimetinib is more clinically effective than vemurafenib in the clinical trial population.

The clinical effectiveness of encorafenib with binimetinib is likely to be similar to dabrafenib with trametinib, but this is associated with uncertainty

3.5 The committee noted that in the absence of trial evidence directly comparing encorafenib with binimetinib against dabrafenib with trametinib, the company did network meta-analyses (NMAs) to indirectly estimate progression-free survival,

overall survival, health-related quality of life and incidence of grade 3 or 4 adverse events. The NMAs included 7 randomised controlled trials of BRAF-inhibitor therapies, all reporting clinical efficacy and safety data, of which 5 reported health-related quality of life data. The committee noted that the company's NMAs show no statistically significant difference between the treatment combinations for investigator-assessed progression-free survival, overall survival, adverse events or health-related quality of life, and that the credible intervals are wide for all base-case and sensitivity analyses. It noted that these results should be viewed with caution because of methodological limitations highlighted by both the company and the ERG. However it acknowledged clinical expert opinion suggesting that the clinical effectiveness of encorafenib with binimetinib is likely to be similar to dabrafenib with trametinib. The committee concluded that the clinical effectiveness of encorafenib and binimetinib is likely to be similar to dabrafenib with trametinib, but this is associated with uncertainty.

Encorafenib with binimetinib may have a favourable safety profile compared with current treatments

3.6 The committee noted that the frequency of adverse events in COLUMBUS is similar for encorafenib with binimetinib, compared with vemurafenib. The trial does not include the relevant comparator (dabrafenib with trametinib), however the committee noted that adverse events for encorafenib with binimetinib were infrequent and serious adverse events were low. The clinical experts stated that encorafenib with binimetinib may offer a more favourable side-effect profile than dabrafenib with trametinib. They explained that some people taking dabrafenib with trametinib develop pyrexia during the first month of treatment, which may lead to hospitalisations and dose interruptions. This did not seem to happen as frequently for encorafenib with binimetinib in COLUMBUS. The committee concluded that encorafenib with binimetinib may have a more favourable adverse-effects profile than dabrafenib with trametinib.

The company's economic model

The company's model is appropriate for decision making

3.7 The company presented a 3 state transition model comparing encorafenib with binimetinib against dabrafenib with trametinib. The progression-free and post-progression states included tunnel states to account for people being 'on' or 'off' primary treatment, reflecting clinical practice. Extrapolation of outcomes beyond the trial period was done using parametric curves that were selected based on best fit to the trial data and visual inspection. The committee concluded that the model structure is appropriate for decision making.

Clinical inputs, utility values and adverse events included in the model are appropriate

3.8 The committee noted that the efficacy and clinical parameters in the model were derived from COLUMBUS data, the company's NMA results and cancer registry data. The committee noted that the clinical effectiveness of encorafenib with binimetinib was based on an indirect comparison against dabrafenib with trametinib, not direct trial evidence (see section 3.5). It acknowledged comments from the ERG that it would be inappropriate to model any difference in efficacy or utility because the company's NMAs show no statistically significant differences between encorafenib with binimetinib and dabrafenib with trametinib for investigator-assessed progression-free survival, overall survival, adverse events and health-related quality of life. The ERG suggested a cost-minimisation approach as their preferred method of analysis, based on an assumption of clinical equivalence. The clinical experts stated that it is biologically plausible that encorafenib with binimetinib and dabrafenib with trametinib are similar in efficacy, in the absence of robust evidence suggesting any differences. However, the committee noted that equivalent efficacy has not been proven. It concluded that the differences in efficacy between treatments using the company's approach are small, and the assumptions in the company's model can be used for decision making alongside the ERG's cost-minimisation approach.

The ERG's correction for relative dose intensity in the company's

base case is appropriate

3.9 In the company model, treatment-related costs are calculated from time on treatment, administration costs, relative dose-intensity multipliers and drug costs. The company assumed that the relative dose-intensity multiplier for encorafenib and binimetinib is lower than for dabrafenib with trametinib. The committee noted that the ERG does not consider this analysis to be robust. The ERG stated that both treatment combinations should have the same multipliers, time on treatment and administration costs (given that they have the same mode of delivery). The ERG therefore corrected the company's base case for relative dose intensity. The committee concluded that this approach is appropriate.

Cost-effectiveness estimates

Taking into account all the commercial arrangements, encorafenib with binimetinib is a cost-effective use of NHS resources

3.10 The committee saw in confidence the company's corrected base case and the ERG's preferred base case using the confidential patient access schemes for encorafenib and binimetinib and for dabrafenib with trametinib. It concluded that encorafenib with binimetinib is a cost-effective use of NHS resources and can be recommended for routine commissioning for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic BRAF V600 mutation-positive melanoma and the healthcare professional responsible for their care thinks that encorafenib with binimetinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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