NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using encorafenib plus binimetinib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2025

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using encorafenib plus binimetinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 24 June 2025
- Second evaluation committee meeting: To be confirmed.
- Details of the evaluation committee are given in section 4

Issue date: May 2025

1 Recommendations

1.1 Encorafenib plus binimetinib should not be used to treat BRAF V600E mutation-positive advanced non-small-cell lung cancer (NSCLC) in adults.

1.2 This recommendation is not intended to affect treatment with encorafenib plus binimetinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

What this means in practice

Encorafenib plus binimetinib is not required to be funded in the NHS in England to treat BRAF V600E mutation-positive advanced NSCLC in adults. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that encorafenib plus binimetinib is value for money in this population.

Why the committee made these recommendations

For this evaluation, the company asked for encorafenib plus binimetinib to be considered only for untreated BRAF V600E mutation-positive advanced NSCLC. This does not include everyone who it is licensed for because the license covers all lines of treatment.

The standard treatment option for BRAF V600E mutation-positive NSCLC is dabrafenib plus trametinib. Dabrafenib plus trametinib is not well tolerated because of side effects such as fever. So, there is an unmet need for treatments for this condition.

Encorafenib plus binimetinib has not been directly compared in a clinical trial with dabrafenib plus trametinib. The results of an indirect comparison suggest encorafenib plus binimetinib may be more effective than dabrafenib plus trametinib. But this is uncertain because of limitations in how the indirect comparison was done.

Because of uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimate for encorafenib plus binimetinib. But it is likely to be above the range that NICE considers an acceptable use of NHS resources. So, encorafenib plus binimetinib should not be used.

2 Information about encorafenib plus binimetinib

Marketing authorisation indication

2.1 Encorafenib (Braftovi; Pierre Fabre Limited) plus binimetinib (Mektovi; Pierre Fabre Limited) is indicated for 'the treatment of adult patients with advanced non-small-cell lung cancer with a BRAF V600E mutation'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for encorafenib.

Price

2.3 Encorafenib costs £1,400 for a 42-pack of 75 mg capsules and binimetinib costs £2,240 per 84-pack of 15 mg tablets (excluding VAT; BNF online accessed May 2025).

2.4 The company has a commercial arrangement for each drug. This makes encorafenib plus binimetinib available to the NHS with a discount and it would have also applied to this indication if encorafenib plus binimetinib had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Pierre Fabre will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Pierre Fabre, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Non-small-cell lung cancer (NSCLC) accounts for around 91% of all lung cancers. People with advanced NSCLC cancer generally have a poor prognosis. The symptoms can be hard to treat, and distressing for the person with the condition and their family members. The BRAF V600E mutation is 1 of many that can stimulate cancer growth. The clinical experts highlighted that the BRAF V600E mutation is not common in NSCLC, and that no more than 2% of all lung cancers will have this mutation. A third to half of all BRAF mutations are V600 mutations, and most BRAF V600 mutations are V600E mutations. The Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund lead) said that around 100 people have first-line dabrafenib plus trametinib each year on the NHS. Because of the rarity of BRAF V600E mutation in NSCLC, the clinical experts highlighted that people with the condition can feel isolated even within the wider lung cancer community. The committee acknowledged that the population with this condition is small, and that BRAF V600E mutation-positive advanced NSCLC has a substantial effect on quality of life.

Treatment options

3.2 There are several NICE-recommended first-line treatments for advanced NSCLC. Dabrafenib plus trametinib is the only NICE-recommended

targeted treatment for treating BRAF V600 mutation-positive advanced NSCLC. (See NICE's technology appraisal guidance on dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced NSCLC; from here, TA898.) Other first-line treatment options include immunotherapy alone, or chemotherapy alone, and immunotherapy plus platinum chemotherapy. People with BRAF V600E mutation-positive advanced NSCLC would generally have dabrafenib plus trametinib as a first-line treatment (see section 3.3). The clinical experts explained that many people with the condition have a poor performance status (that is, how well they are and what treatments they can tolerate). So, they are not offered active treatment, and instead have palliative care. The clinical experts highlighted that dabrafenib plus trametinib is associated with a high burden of side effects, leading to a high use of emergency care with substantial healthcare resource use. They noted that the most common side effect is pyrexia (fever), which leads to many people stopping treatment, even if the treatment is working. The clinical experts explained that pyrexia is also associated with an increased use of antibiotics to treat suspected sepsis, and additional chest scans may also be needed. Other side effects include nausea, abdominal pain and rash. The committee noted the various treatment options available and acknowledged that there is an unmet need because of side effects caused by current treatment options.

Comparators and line of treatment

3.3 The company positioned encorafenib plus binimetinib at first line only, and compared it with dabrafenib plus trametinib. Encorafenib plus binimetinib has a marketing authorisation for all lines of treatment. The clinical experts said that genomic testing is routinely available in the NHS. So, people whose NSCLC has a BRAF V600E mutation should be offered dabrafenib plus trametinib. The Cancer Drugs Fund lead explained that people who have had dabrafenib plus trametinib at first line would not be eligible to have encorafenib plus binimetinib at second line. But they also said that this does not apply if someone has stopped dabrafenib plus

trametinib because of toxicity alone (without disease progression). NHS England would still think that this is first line, and would allow them to switch to encorafenib plus binimetinib. The committee thought that it was unlikely that encorafenib plus binimetinib would be used at second line. It noted that the treatment switching at first line as described by the Cancer Drugs Fund lead was not present in the model. The committee thought that it was unclear what effect this might have on the cost-effectiveness analyses. It concluded that dabrafenib plus trametinib was the most relevant comparator in this evaluation. It also concluded that the first-line positioning of encorafenib plus binimetinib in the treatment pathway was appropriate.

Clinical effectiveness

PHAROS clinical trial

3.4 The clinical-effectiveness evidence for encorafenib plus binimetinib came from PHAROS, a phase 2 single-arm trial. This enrolled people with stage 4 NSCLC with a BRAF V600E mutation. Trial outcomes included overall response rate, progression-free survival (PFS) and overall survival (OS). The trial was a multicentre international study that did not include sites in England. There were 2 cohorts:

- One cohort had had no prior anticancer treatment for advanced or metastatic disease and was defined as 'treatment naive' (n=59).
- The other cohort had had prior anticancer treatment at first line for advanced or metastatic disease (n=39).

People in each cohort had 450 mg of encorafenib once daily plus 45 mg of binimetinib twice daily until their cancer progressed or there were unacceptable levels of toxicity. In the treatment-naive cohort, the median PFS was 30.2 months (95% confidence interval [CI] 15.7 to not estimable). Median OS was not estimable because of immature data. The clinical-effectiveness evidence from the treatment-naive cohort

was used to inform the cost-effectiveness evidence for encorafenib plus binimetinib as first-line treatment (see section 3.6, section 3.9 and section 3.10). The Cancer Drugs Fund lead highlighted that the median age of people having dabrafenib plus trametinib in the NHS is 71 years. This is higher than the median age of the treatment-naive cohort, which was 68 years in PHAROS. Also, the Cancer Drugs Fund lead noted that PHAROS only included people with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1. Also, in cohort C of the BRF113928 trial, 1 person enrolled had an ECOG-PS of 2. But about 25% of people who have first-line dabrafenib plus trametinib in the NHS have an ECOG-PS of 2. The clinical experts explained that ECOG-PS is a very strong prognostic factor. The committee noted the efficacy results from PHAROS. It thought that the mismatch in ECOG-PS2 between the trial and NHS practice was a generalisability concern that was associated with some uncertainty.

IFCT clinical trial

3.5 The company submitted additional supporting evidence for the clinical effectiveness of encorafenib plus binimetinib from IFCT, a phase 2 single-arm trial. This enrolled people with stage 4 NSCLC with a BRAF V600E mutation. Trial outcomes included overall response rate, PFS and OS. The trial was done across 36 sites in France. There were 2 cohorts:

- One cohort had had no prior anticancer treatment for advanced or metastatic disease and were defined as 'treatment naive' (n=64).
- The other cohort had had prior anticancer treatment at first line for advanced or metastatic disease (n=59).

People in each cohort had 450 mg of encorafenib once daily plus 45 mg of binimetinib twice daily. The exact results of this trial cannot be reported here because the company considers them confidential. The committee noted that the OS results were similar to those in PHAROS but PFS was lower in IFCT compared with PHAROS. The results from

the treatment-naive cohort in IFCT were used to inform scenarios within the company model (see section 3.6). The company said that there was a higher proportion of people with brain metastases in IFCT compared with PHAROS, but that otherwise the trials were similar. A clinical expert agreed with this characterisation. The clinical experts highlighted that the presence of brain metastases would likely cause the cancer to spread quicker and possibly be less responsive to treatment. This is because of reduced drug exposure in the brain. One clinical expert also thought that, because IFCT recruited people from numerous centres in a single country, it might have been more likely to have 'real-world patients'. That is, it might have included people representing the wider population as opposed to a group of highly selected people often present in large global clinical trials. They thought that, for this reason and because France has a similar healthcare system to the UK, the IFCT trial might have been more like UK clinical practice than an international clinical trial including people from Korea and the US. The committee noted that the prevalence and mortality of lung cancer is higher in France than in the NHS. So, while, it was plausible that IFCT represented a similar population to the UK, this should be treated with caution. It concluded that IFCT was a useful source of information on the efficacy of encorafenib plus binimetinib. But it requested a comparison between the baseline characteristics between PHAROS and IFCT.

Indirect treatment comparison

Matching-adjusted indirect comparison with dabrafenib plus trametinib

3.6 There were no trials directly comparing encorafenib plus binimetinib with dabrafenib plus trametinib. So, the company did a unanchored matching-adjusted indirect comparison (MAIC) to establish the relative efficacy. It did this by adjusting the treatment-naive cohort from PHAROS to better match the treatment-naive cohort of BRF113928. This was a phase 2 single-arm trial assessing dabrafenib plus trametinib and was used for the

source of clinical-effectiveness data in TA898. It included people with stage 4 NSCLC with a BRAF V600E mutation. Cohort C of BRF113928 consisted of 36 people who had no prior anticancer treatment for metastatic disease.

The company noted that the matching for the MAIC reduced the effective sample size of PHAROS by about 25%, with the weighted population representing 44 people instead of the original 59. The company adjusted for 7 prognostic factors (age, gender, ECOG status, smoking status, race, histology and presence of brain metastases). After adjustment, encorafenib plus binimetinib was associated with better outcomes compared with dabrafenib plus trametinib:

- a non-statistically significant reduction in mortality of 45% (hazard ratio [HR] 0.55; 95% CI 0.30 to 1.01)
- a statistically significant reduction in disease progression by 53% (HR 0.47; 95% CI 0.26 to 0.85).

The clinical experts thought that there was likely no difference in efficacy between dabrafenib plus trametinib and encorafenib plus binimetinib while people are on treatment. But they said that, for dabrafenib plus trametinib, toxicity is higher (see section 3.2). So, there would be more treatment stopping and reduced drug exposure compared with encorafenib plus binimetinib. They highlighted that stopping treatment would be associated with quicker progression, which would also affect OS. One clinical expert experienced in using encorafenib plus binimetinib in people with a BRAF V600 mutation-positive melanoma highlighted that, in their experience, about 33% of people are unable to tolerate dabrafenib plus trametinib. But they said that this figure was less than 10% with encorafenib plus binimetinib. The Cancer Drugs Fund lead explained that, in people with BRAF V600 mutation-positive advanced or metastatic melanoma eligible for treatment, around 67% access encorafenib plus binimetinib and around

33% access dabrafenib plus trametinib. They thought that this was because of the differing toxicity profiles.

The company presented a scenario that pooled data from IFCT with data from PHAROS to do a MAIC to compare encorafenib plus binimetinib with dabrafenib plus trametinib. The exact results of the pooled analysis are considered to be confidential by the company and cannot be reported here.

The committee noted that there was a difference in PFS between the pooled trial data and the data from PHAROS alone that was used to inform the MAIC. It thought that this was likely because PFS was lower in IFCT that in PHAROS. The committee thought that, given the small size of both trials, it was important to use all the available evidence. So, it thought that IFCT should also inform the estimates of relative efficacy. But the committee raised concerns about whether appropriate methods were used to pool the PHAROS and IFCT data in the MAIC analysis. It said that it was unclear whether the naive pooling done by company was the most appropriate approach. The company explained that the 2 studies were pooled naively to retain sample size. The committee concluded that it would like to see alternative ways of pooling the data for the MAIC and an exploratory scenario using only the IFCT data to model relative effectiveness. This is to examine what effect the lower PFS (see section 3.5) seen in IFCT might have on the estimates of cost effectiveness.

Covariates included in the MAIC

3.7 The MAIC was unanchored, which implicitly assumed that all effect modifiers and prognostic factors had been adjusted for. It could only adjust for baseline variables that had been reported in both studies. The analysis accounted for the following effect modifiers and prognostic covariates:

- age
- gender
- race
- smoking status
- ECOG-PS
- histology
- presence of brain metastases
- line of treatment for second-line analysis only.

The company did a sensitivity analysis to explore the impact of only adjusting for covariates that the company's clinical experts thought were key prognostic factors that affected the MAIC results. It presented results that were adjusted for ECOG-PS and smoking status only. This population adjustment did not affect the results compared with the unadjusted comparison. The exact results of the sensitivity analysis are considered to be confidential by the company and cannot be reported here. The EAG highlighted that there was a lack of adjustment for some potentially important prognostic variables in the MAIC, including:

- concomitant mutation in P13K pathway
- presence of metastasis in the thoracic cavity
- PD-L1 expression of 1% or more
- presence of liver metastases.

The clinical experts explained that brain and liver metastases were important prognostic variables. They thought that the failure to adjust for liver metastases might have affected the reliability of the MAIC results. The company said that there was a lack of available data for thoracic cavity and liver metastasis for dabrafenib plus trametinib. This was why they were not adjusted for in the MAIC analysis. The committee highlighted that data was available for these 2 prognostic variables in TA898. It concluded that lack of adjustment for some

prognostic variables was a source of uncertainty in the company's MAIC. It added that it would like to have seen liver metastases adjusted for in the base-case and scenario analyses adjusting for all possible prognostic factors available.

Economic model

Company's modelling approach

3.8 To model the cost effectiveness of encorafenib plus binimetinib and dabrafenib plus trametinib, the company used a partitioned survival model with 3 health states: 'progression free', 'progressed disease' and 'death'. The efficacy of encorafenib plus binimetinib was modelled using extrapolations of the unadjusted PFS and OS curves from PHAROS (see section 3.9). The efficacy of dabrafenib plus trametinib was modelled by applying a hazard ratio from the base-case MAIC to the PFS and OS curves for encorafenib plus binimetinib (see section 3.6 and section 3.11). The company chose a cycle length of 1 week with a half-cycle correction and a lifetime time horizon of 36 years. The company initially informed the baseline characteristics from the unadjusted PHAROS population. The EAG requested a scenario in which the baseline characteristics were informed from the MAIC base-case population. The committee noted that baseline characteristics should be from the same source as the intervention efficacy. It concluded that it would take both approaches into account in its decision making. It also noted that there were large differences between deterministic and probabilistic results, and said that it would like the company and EAG to explore this. The committee concluded that a partitioned survival model was appropriate for decision making.

Modelling long-term OS and PFS for encorafenib plus binimetinib

3.9 The company selected the exponential distribution to extrapolate both PFS and OS from the Kaplan–Meier curves from PHAROS. It thought that this provided a good statistical fit. It also thought that it was consistent

with clinical expert opinion saying that few people would be progression free at 5 years and 10 years, or alive at 20 years. The EAG noted that the company provided limited clinical expert opinion to justify the curve choices. It also explained that the smoothed hazard curves for OS and PFS decreased over time. This showed a non-constant hazard, which was inconsistent with the exponential distribution. The exponential distribution predicted the lowest OS (41%) at 5 years. The clinical experts thought that this was implausible and would not expect 5-year survival to be this high. The committee thought that none of the long-term OS estimates were plausible. It also thought that the PFS estimates for encorafenib with binimetinib were uncertain. It concluded that it would like to see alternative modelling approaches for modelling long-term OS and PFS, such as flexible parametric modelling. It added that it would like to see detailed clinical expert elicitation to justify the choice of preferred curves.

Modelling relative treatment effectiveness for dabrafenib plus trametinib

3.10 The company modelled PFS and OS for dabrafenib plus trametinib by applying hazard ratios from the base-case MAIC (see section 3.6) to the extrapolated PFS and OS curves for encorafenib plus binimetinib (see section 3.9). This approach needed an assumption of proportional hazards between the 2 regimens. The company presented log-log survival curves for both regimens in the model. It noted that, for OS, the 2 log-log survival curves crossed in the first half of the observation period but were parallel in the second half. It said that this was likely because there were few events for encorafenib plus binimetinib at the start of the trial. The company also plotted Schoenfeld residuals and thought that they showed a flat pattern that further supported the assumption of proportional hazards. The EAG agreed that it was reasonable to assume proportional hazards. The committee thought that it was not unusual to see crossing of log-log plots at the start or end of trials when there were a small number of events. It concluded that the proportional hazards assumption was likely to be appropriate but that some uncertainty remained. The committee recalled that the company had not presented plausible

extrapolations of long-term OS and PFS for encorafenib plus binimetinib (see section 3.9). It noted that, under the proportional hazards' assumption, the modelling of dabrafenib plus trametinib was dependent on these estimates. It concluded that it would need to reassess proportional hazards modelling for dabrafenib plus trametinib if new modelling of encorafenib plus binimetinib were presented. But it also requested further analysis from the company to explore independent fitting of parametric curves to each arm of the model.

Modelling time to treatment discontinuation for encorafenib plus binimetinib

3.11 Time to treatment discontinuation (TTD) data was not explicitly collected in PHAROS. The EAG thought that the company used appropriate methods to get TTD for encorafenib plus binimetinib. The company fitted parametric curves to extrapolate TTD for encorafenib plus binimetinib and selected the exponential curve for its base case. The committee thought that long-term TTD estimates for encorafenib with binimetinib were plausible but uncertain. It concluded that it would like to see alternative modelling approaches explored, such as flexible parametric modelling, and detailed expert elicitation to justify the choice of preferred curves.

Modelling TTD for dabrafenib plus trametinib

3.12 In its base case, the company:

- assumed that TTD for dabrafenib plus trametinib was equal to PFS because there was no publicly available TTD data for dabrafenib plus trametinib
- provided scenarios fitting exponential curves using the median TTD from BRF113928 (10.6 months)
- applied the hazard ratio between TTD and PFS for encorafenib plus binimetinib from PHAROS to PFS from BRF113928.

The company thought that the hazard-ratio scenario was not

appropriate because it underestimated the median TTD from BRF113928. So, it thought that it would underestimate costs for dabrafenib plus trametinib. The EAG's base case used the hazard-ratio approach. It thought that this was appropriate because the 2 treatments had similar mechanisms of action and might reasonably have a similar relationship between TTD and PFS. The clinical experts confirmed that many people stop treatment, even if their cancer has not progressed, because side effects are not tolerated (see section 3.2). They said that assuming TTD is equal to PFS was too simplistic. The committee thought that it was not plausible to assume that TTD is equal to PFS. It concluded that either the scenario plotting an exponential curve through the median from BRF113928 or the scenario applying a hazard ratio from PHAROS would be more appropriate. It concluded that it would consider both scenarios in its decision making or would consider an alternative scenario that gives plausible results with clinical expert validation.

Treatment-effect waning

3.13 The company's base case assumed that there was no treatment-effect waning beyond the observed trial. The company said that encorafenib plus binimetinib has a similar mechanism of action as dabrafenib plus trametinib. It also noted that no treatment-effect waning was assumed in TA898. It highlighted that the observed hazards for encorafenib plus binimetinib and for dabrafenib plus trametinib for OS and PFS did not converge. In fact, they diverged for PFS. The company also thought that people may benefit from a BRAF inhibitor or a MEK inhibitor after stopping treatment. It presented a scenario that modelled treatment-effect waning starting from the point of maximum follow up of the PHAROS trial. That is, the hazard ratio between the 2 treatments returned to 1 after the maximum follow up of the PHAROS trial. The EAG agreed that there was no evidence of treatment-effect waning during PHAROS. But it highlighted that there was still uncertainty about whether this assumption was applicable beyond the observed data period. The clinical experts said that

they did not expect treatment effect to wane in the long term. But they noted that it was difficult to comment on what would happen with the limited evidence available. The committee thought that it was uncertain whether treatment effect would wane in the long term. It concluded that it would like to see exploratory modelling of various treatment-effect waning scenarios.

Utility values

3.14 The company applied the same health-state utility values as used in TA898, to inform 'progression-free' and 'progressed-disease' health states. These values were taken from Chouaid et al. (2013), a cross-sectional study that measured health states in advanced NSCLC. The company also presented a scenario that took the estimated utility values from IFCT, which were based on a mixed model with repeated measures (MMRM). A second scenario was presented by the company that applied the progressed-disease decrement from TA898 (0.04) to the IFCT MMRM derived progression-free utility value. The EAG raised concerns with the utility values from Chouaid et al., explaining that:

- the study had a high rate of non-random drop out because of incomplete EQ-5D data
- the progression-free utility value at first line was lower than progression-free utility at second line.

The committee acknowledged the limitations of the utility values from the Chouaid et al. But it noted that these values had been accepted in the evaluation for dabrafenib plus trametinib, and were likely to be appropriate for decision making. The committee also recalled that it would like to see IFCT data used to generate the estimates of relative efficacy. It concluded that it might also be appropriate to use the accompanying utility values from IFCT.

Costs

Cost of modelling per-pack approach

3.15 The company chose to model drug acquisition costs of oral treatments per milligram. It provided a scenario that applied a per-pack costing approach for oral treatments for 28 days. The EAG highlighted that the per-pack costing approach is in line with NICE process and methods. But it modelled this per-pack approach weekly as a per-cycle cost. The committee noted that NICE methods requires that oral treatments should be modelled on a per-pack basis. It also thought that drugs would be dispensed over a longer time frame and weekly dispensing would be unlikely in NHS practice. The committee concluded that a per-pack costing approach should be applied when modelling drug acquisition costs of oral treatments. It also thought that this should be applied every 28 days because this would likely reflect dispensing in NHS clinical practice.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 The committee concluded that the company's overall model structure was acceptable for decision making (see section 3.8). It noted that the company's and EAG's base-case incremental cost-effectiveness ratios (ICERs) were substantially above NICE's cost-effectiveness threshold. It recalled that its preferred assumptions were:

- encorafenib plus binimetinib positioned for first-line use only (see section 3.3)
- dabrafenib plus trametinib as the most appropriate comparator (see section 3.3)
- drug acquisition costs modelled per pack and applied every 28 days (see section 3.15).

The committee acknowledged that, even when its preferred

assumptions were incorporated into the model, substantial uncertainty remained, including on:

- reliance on an unanchored MAIC, and missing prognostic variables in the MAIC (see section 3.6 and section 3.7)
- modelling of long-term OS, PFS (see section 3.9) and TTD for encorafenib plus binimetinib (see section 3.10)
- relative treatment effectiveness and TTD for dabrafenib plus trametinib (see section 3.11 and section 3.12)
- source of most appropriate health-state utility values (see section 3.14)
- treatment-effect waning (see section 3.13).

The committee would like to see the following analyses and further evidence to help it to decide on the cost effectiveness of encorafenib plus binimetinib:

- an additional MAIC scenario:
  - for IFCT alone
  - to explore alternative approaches for the pooled data in the MAIC analysis because naive pooling might not be appropriate (see section 3.6 and section 3.7)
- updated MAICs adjusting for liver metastasis and exploring all possible available variables (see section 3.7)
- exploration of differences between deterministic and probabilistic results (see section 3.8)
- use of baseline characteristics from the same source as for the intervention efficacy (see section 3.8)
- exploration of independent fitting of parametric curves to extrapolate PFS and OS in each arm (see section 3.10)
- alternative modelling approaches for OS (see section 3.9), PFS (see section 3.9) and TTD (see section 3.10) that might include flexible parametric modelling and provide full justification and expert elicitation for the choice of preferred curves

- alternative modelling approaches and detailed clinical expert input for TTD for encorafenib plus binimetinib (see section 3.12)
- further exploratory analyses that present different treatment-effect waning assumptions (see section 3.13).

Acceptable incremental cost-effectiveness ratio

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee also considered the toxicity of targeted treatment options for this mutation and the emotional burden on people with BRAF V600E mutation-positive NSCLC and their carers (see section 3.2). It noted the rarity of BRAF V600E mutation-positive NSCLC and the difficulties that rarity can create in generating evidence (see section 3.1) and also the high level of uncertainty (see section 3.16). The committee was unable to identify a threshold ICER. This was because an acceptable ICER is intended to account for unresolvable uncertainty in the model and there were additional analyses needed that might resolve some uncertainty in the modelling. The committee concluded that it would reconsider the ICER threshold at its second meeting. This would take into account any new analyses presented, unmet need and the rarity of BRAF V600E advanced NSCLC.

Other factors

Equality

3.18 The committee did not identify any equality issues.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of encorafenib plus binimetinib, and identified additional benefits not captured in the economic modelling. It recalled that encorafenib plus binimetinib is better tolerated than dabrafenib plus trametinib because it does not cause pyrexia as often. This results in few hospital admissions for people having encorafenib plus binimetinib. This is then associated with a reduced burden on emergency care, less use of antibiotics to treat suspected sepsis and fewer chest scans.

Conclusion

Recommendation

3.20 Because of the uncertainty in the clinical- and cost-effectiveness evidence, the committee was not able to establish its preferred cost-effectiveness estimates for encorafenib plus binimetinib. It thought that the most plausible estimates were likely to be higher than the range NICE considers to be cost-effective. The committee concluded that additional evidence is needed, and that encorafenib plus binimetinib should not be used to treat BRAF V600E mutation-positive advanced NSCLC in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in the technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Professor Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

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

Alice Pritchard

Technical lead

Samuel Slayen

Technical adviser

Louise Jafferally

Project manager

Ross Dent

Associate director

ISBN: [to be added at publication]