NICE National Institute for Health and Care Excellence

NICE guidance

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

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.

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1 Recommendations

1.1 Encorafenib plus binimetinib can be used as an option to treat BRAF V600E mutation-positive advanced non-small-cell lung cancer (NSCLC) in adults, only if:

- it is used at first line, and
- the company provides them according to the commercial arrangements.

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 healthcare professional consider it appropriate to stop.

What this means in practice

Encorafenib plus binimetinib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. It should be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that encorafenib plus binimetinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

For this evaluation, the company asked for encorafenib plus binimetinib to be considered only for untreated (that is, at first line) BRAF V600E mutation-positive advanced NSCLC. This does not include everyone who it is licensed for because the licence 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 that encorafenib plus binimetinib may be more effective than dabrafenib plus trametinib.

After taking into account the clinical evidence and impact of its uncertainty, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, encorafenib plus binimetinib can 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 commercial arrangements for encorafenib and binimetinib. These make encorafenib and binimetinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on the company's webpage on sustainable development.

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 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 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, chemotherapy alone or 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, a measure of 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 economic 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 trial 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 a first-line treatment only. 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. The committee noted the efficacy results from PHAROS and the immaturity of the data. It agreed that seeing updated data from PHAROS would support decision making.

Updated data from PHAROS and generalisability

3.5 At draft guidance consultation, the company provided updated clinical-effectiveness evidence for encorafenib plus binimetinib from an additional data cut from PHAROS in March 2025. This provided updated data on OS and time to treatment discontinuation (TTD) for encorafenib plus binimetinib. The exact results cannot be reported here because the company considers them confidential. Median OS was reached in the updated data cut-off. The company highlighted that 5-year OS from PHAROS was higher than what its clinical experts would expect in clinical practice. The committee noted that there were substantial differences in certain prognostic factors between both the PHAROS trial and NHS clinical practice populations. Notably more people had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 in PHAROS than in NHS clinical practice and this might overestimate the treatment effect observed in PHAROS for encorafenib plus binimetinib. The Cancer Drugs Fund lead noted that PHAROS only included people with an ECOG PS of 0 or 1. The clinical experts explained that ECOG PS is a very strong prognostic factor and people with an ECOG PS of 2 would likely have worse outcomes. The NHS England Cancer Drugs Fund lead explained that PHAROS did not recruit people with an ECOG PS score of 2. They said that NHS England Blueteq commissioning criteria are written to match clinical trial criteria. So, any commissioning criteria for encorafenib plus binimetinib would likely not include an ECOG PS of 2. The committee also noted that there was a low proportion of people with brain metastases in PHAROS, and this number might be higher in NHS clinical practice. It noted these were important prognostic factors. At draft guidance consultation, the company highlighted that the rarity of the condition impacted trial recruitment and therefore generalisability. The committee noted that in PHAROS there was:

- a higher proportion of people with an ECOG PS score of 0 than would be present in NHS practice
- potentially a lower proportion of people with brain metastases.

The committee also noted that data on liver metastases, another important prognostic factor, was neither collected in PHAROS nor available from NHS clinical practice. The committee concluded that there were substantial uncertainties linked to the generalisability of the clinical trial data to NHS clinical practice.

IFCT clinical trial

3.6 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 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. 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, for this reason and because France has a similar healthcare system to the UK, that IFCT 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.

Indirect treatment comparison

Matching-adjusted indirect comparison with dabrafenib plus trametinib

3.7 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 relative efficacy estimates. Data for dabrafenib plus trametinib came from a study by Planchard et al, (from here BRF113928), a phase 2 single-arm trial which included people with stage 4 NSCLC with a BRAF V600E mutation. The company adjusted the treatment-naive cohort from PHAROS to better match the treatment-naive cohort of BRF113928. 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 PS, 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. 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 for 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.

At the first committee meeting, 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 than 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 3.6) seen in IFCT might have on the estimates of cost effectiveness.

Updated indirect treatment comparisons

3.8 At draft guidance consultation, the company presented updated indirect treatment comparisons that used the most recent March 2025 data cut (see section 3.5). It presented:

- a MAIC using PHAROS compared with BRF113928
- a MAIC using IFCT compared with BRF113928, as requested by committee (see section 3.7)

- a fixed effect meta-analysis using pooled MAIC-adjusted hazard ratios from PHAROS and IFCT compared with BRF113928.

  The company's fixed effect meta-analysis replaced the naively pooled PHAROS plus IFCT MAIC presented at the first committee meeting (see section 3.7). This MAIC was no longer available in the model for decision making. Both the new MAICs and the meta-analysis were available with:

- a base-case analysis adjusting for 7 available covariates
- a sensitivity analysis that only adjusted for smoking status and ECOG PS (see section 3.9).

  The fixed effect meta-analysis approach used by the company combined the adjusted hazard ratios from the base case and the sensitivity MAICs. The company maintained its original base case, which used PHAROS as the source of clinical effectiveness for OS and PFS for encorafenib plus binimetinib. The EAG noted that having a pooled hazard ratio from PHAROS and IFCT led to an increased sample size. So, it preferred this approach. The committee highlighted that the company's chosen meta-analysis relied on the proportional hazards assumption being accepted for both trial comparisons, which was uncertain (see section 3.11). It also said a fixed effect meta-analysis may have underestimated the uncertainty from pooling 2 trials. But it highlighted that the results from the previous pooling attempt presented at the first committee meeting were similar to the results from the fixed effect meta-analysis approach. So, the committee was reassured that the company had explored the uncertainty. It concluded that it would use the meta-analysis pooled hazard ratios for OS and PFS from PHAROS and IFCT compared with BRF113928 for decision making. This was because it increased the sample size in the analysis compared with using 1 trial. But it noted that the reliance on proportional hazards increased the residual uncertainty (see section 3.11). It also noted that not all covariates were adjusted (see section 3.9). This meant that the company's fixed effect meta-analysis was uncertain and the uncertainty may be greater than what was estimated.

Covariates included in the MAIC

3.9 The MAICs were 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 greatly 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 in both meetings 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. 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.

At draft guidance consultation, the company stated that the liver metastasis and M1a (meaning cancer has spread to both lungs, or there is cancer in the outer lining of the lung or the fluid around the lungs) prognostic variables could not be adjusted for because these were not collected in PHAROS. So, the adjusted factors in the analysis were unchanged from the original MAIC analysis. The clinical experts confirmed that brain metastasis was the most important prognostic variable, followed by liver metastasis. The committee concluded that it would use the base-case MAIC meta-analysis (see section 3.8). But it also highlighted that uncertainty remained in the indirect treatment comparison analyses because not all prognostic variables could be adjusted for.

Economic model

Company's modelling approach

3.10 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 committee agreed that a partitioned survival model was appropriate for decision making. The efficacy of encorafenib plus binimetinib was modelled using extrapolations of the unadjusted PFS and OS curves from PHAROS (see section 3.12). 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 3.8 and section 3.13). 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.

Assessment of proportional hazards

3.11 For the first committee meeting, the company modelled PFS and OS for dabrafenib plus trametinib by applying hazard ratios from the base-case MAIC (see section 3.7) to the extrapolated PFS and OS curves for encorafenib plus binimetinib (see section 3.12). 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 for the PHAROS trial comparison but that some uncertainty remained. It noted that the modelling of dabrafenib plus trametinib was dependent on the proportional hazards assumption. The committee requested further analysis from the company to explore independent fitting of parametric curves to each arm of the model.

At draft guidance consultation, the company presented updated log-log survival curves and Schoenfeld residuals for both encorafenib plus binimetinib and dabrafenib plus trametinib. It did this for both the updated March 2025 PHAROS OS data cut (see section 3.5) and IFCT (see section 3.6). The EAG confirmed that it was willing to accept proportional hazards using the PHAROS data. But it thought that there was greater uncertainty around this assumption using the

IFCT OS data. This was because the amount of statistical significance of the Schoenfeld residuals decreased when using IFCT. Also, there was crossing of the log-log survival curves later in the trial follow up when there were more events. The committee noted that, for the results of the company's updated meta-analysis (see section 3.8) to be valid, the proportional hazards assumption was needed for both trial comparisons. It thought that the assumption was likely to hold for the comparison between PHAROS and BRF113928. It also thought that it might hold for the comparison between IFCT and BRF113928 but that this was much less certain. The committee concluded that it would accept the proportional hazards assumption for both comparisons with dabrafenib plus trametinib. But it thought that this was associated with uncertainty because of the IFCT comparison.

Modelling long-term OS and PFS for encorafenib plus binimetinib

3.12 At the first committee meeting, 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 and 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 clinical-expert opinion provided by the company did not help to differentiate the extrapolated 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 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 plus 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.

At draft guidance consultation, the company presented results for long-term OS and PFS, including independently fitting parametric curves to extrapolate OS and PFS. It also presented alternative modelling for OS and PFS that included flexible

parametric modelling. Because the committee accepted the proportional hazards assumption (see section 3.11), the independently fitted curves were not relevant. The company provided OS and PFS extrapolations based on both the March 2025 data cut from PHAROS (see section 3.5) and IFCT (see section 3.6). The company maintained its original base case, using the updated OS data. It selected the exponential distribution to extrapolate both PFS and OS from the Kaplan–Meier curves from PHAROS because it provided the most conservative estimates. The company provided interviews with clinical experts to inform the choice of curve.

The EAG highlighted that predicted OS varied among clinical experts, with 5-year OS being predicted to be between 10% to 25% for encorafenib plus binimetinib. The EAG noted the PHAROS 5-year OS was much higher than the average clinical-expert-predicted value of 18%. The EAG noted that all OS extrapolations for encorafenib plus binimetinib produced higher survival estimates than those estimates by clinical experts. The EAG selected the exponential distribution in line with the company, despite it being suboptimal. This was because it provided the most conservative estimate for long-term OS for encorafenib plus binimetinib. Also, its 10-year OS predictions aligned with the estimates from clinical experts. The EAG noted that, for PFS, all extrapolations for encorafenib plus binimetinib overestimated 5-year PFS compared with clinical-expert opinion. The clinical experts highlighted that the extrapolation estimates provided were uncertain and might overpredict expected survival in the short term, but long-term OS appeared more accurately predicted.

The committee noted that the ability to extrapolate from the naively pooled PHAROS and IFCT Kaplan–Meier data had been removed from the model in the consultation period. But it thought this would have been a useful analysis to see. In the absence of this, the committee concluded that it would prefer to extrapolate from the PHAROS-only Kaplan–Meier data. The committee recalled the uncertainty around the 5-year results from PHAROS and how the results might not be generalisable to NHS clinical practice (see section 3.5). It concluded that the extrapolations were associated with uncertainty because of concerns about the generalisability of PHAROS.

Modelling relative treatment effectiveness for dabrafenib plus trametinib

3.13 The committee accepted the proportional hazards assumption (see section 3.11). It selected its preferred indirect treatment comparison as the meta-analysis of adjusted PHAROS and IFCT data compared with BRF113928 (see section 3.8). So, in its preferred base case, the committee modelled dabrafenib plus trametinib by applying the hazard ratios for PFS and OS from the meta-analysis to the exponential distribution.

Modelling TTD for encorafenib plus binimetinib

3.14 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 plus 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.

At draft guidance consultation, the company presented results that provided updated parametric curves to extrapolate TTD using the updated March 2025 data cut from PHAROS. It also presented results of extrapolation of TTD data using flexible parametric modelling. The company maintained its original base case and used an exponential curve. The EAG highlighted that the smoothed hazard curves for TTD declines over time. It said that this showed non-constant hazards that were not captured by the exponential distribution. It also highlighted that the exponential distribution overestimated 5-year TTD but underestimated TTD at 10 and 15 years compared with clinical-expert prediction. The EAG noted that the spline odds (2 knots) model overestimated TTD at 5 years, but the values predicted at 10 and 15 years were more closely aligned to clinical-expert opinion, so it used this as its base case. The committee concluded that it preferred the spline odds (2 knots) model to model TTD for encorafenib plus binimetinib because the predicted TTD more closely aligned with clinical-expert predictions.

Modelling TTD for dabrafenib plus trametinib

3.15 There was no publicly available TTD data for dabrafenib plus trametinib, so the company provided a range of scenarios to model TTD for dabrafenib including:

- assuming that TTD for dabrafenib plus trametinib was equal to PFS
- providing scenarios fitting exponential curves using the median TTD from BRF113928 (10.6 months)
- applying 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 agreed 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.

  At draft guidance consultation, the company presented additional scenarios to extrapolate TTD for dabrafenib plus trametinib using 2 studies: Swalduz et al. (2024) and Auliac et al. (2020). Swalduz et al. was a real-world efficacy study investigating the clinical effectiveness of dabrafenib plus trametinib in a BRAF V600E mutation-positive NSCLC population. Auliac et al. was a retrospective multicentre study investigating the clinical effectiveness of dabrafenib plus trametinib in a real-world setting. The scenarios explored:

- fitting an exponential curve through the median treatment duration from Swalduz et al. and Auliac et al. weighted by sample size
- assuming the median treatment duration was similar to median PFS by the investigator in real-world studies

- assuming equivalence of treatment duration between dabrafenib plus trametinib and encorafenib plus binimetinib.

  The company revised its base case and presented a weighted average treatment duration from Swalduz et al. and Auliac et al. The EAG highlighted that these studies had been completed in France and that the baseline characteristics were different compared with the baseline characteristics in BRF113928. The committee concluded that it preferred applying a hazard ratio between PFS and TTD for encorafenib plus binimetinib to PFS for dabrafenib plus trametinib (as in the EAG's base case). This was because this method used data from the trials informing clinical effectiveness and because the similarity between the 2 trials was known. But, if data from other trials was used, it was not known how similar these populations were.

Treatment-effect waning

3.16 The company's base case assumed that there was no treatment-effect waning beyond the observed trial data. The company said that encorafenib plus binimetinib has a similar mechanism of action to 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 PHAROS. That is, the hazard ratio between the 2 treatments returned to 1 following a constant 2-year waning duration that began at the maximum follow up of PHAROS. 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.

At draft guidance consultation, the company presented an additional scenario that applied a treatment-effect waning at the maximum follow up of PHAROS for a duration of 3 months. After this, the risks were equivalent in both arms. Clinical experts consulted by the company stated that they did not think treatment-effect waning was relevant. The company also updated its original scenario that included the PHAROS March 2025 data cut. The EAG aligned with the company. It agreed that there was no evidence of treatment-effect waning in the observed period, although noted that predicting what might happen afterwards was difficult. The committee did not see a plausible rationale that there would be treatment-effect waning and so concluded that modelling explicit treatment-effect waning was not appropriate.

Utility values

3.17 The company applied the same health-state utility values as used in TA898, to inform the '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 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. At draft guidance consultation, the company confirmed that no more appropriate data to inform health-state utility values had been identified. The committee noted that the choice of utility had a very small effect on the cost-effectiveness results. It concluded that the most

appropriate source to inform health-state utility values was Chouaid et al. and that this would align with TA898.

Costs

Cost of modelling per-pack approach

3.18 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's processes and methods as detailed in section 3.5 of NICE's user guide for company evidence submission template. But it modelled this per-pack approach weekly as a per-cycle cost. The committee noted that NICE's processes and 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

3.19 The committee concluded that the company's overall model structure was acceptable for decision making (see section 3.10). It recalled that its preferred assumptions were:

- positioning encorafenib plus binimetinib for first-line use only (see section 3.3)
- that dabrafenib plus trametinib is the most appropriate comparator (see section 3.3)

- using exponential distribution to extrapolate long-term OS and PFS from the PHAROS-only Kaplan–Meier data (see section 3.12)
- using the proportional hazards assumption for modelling dabrafenib plus trametinib (see section 3.11)
- using a pooled hazard ratio from the meta-analysis for OS and PFS from PHAROS and IFCT compared with BRF113928 to model relative effectiveness of dabrafenib plus trametinib (see section 3.8)
- using the spline odds (2 knots) model to model TTD for encorafenib plus binimetinib (see section 3.14)
- applying a hazard ratio between PFS and TTD for encorafenib plus binimetinib to PFS for dabrafenib plus trametinib (see section 3.15)
- not modelling treatment-effect waning because it is unlikely to be appropriate (see section 3.16)
- using health-state utility values from TA898 to inform 'progression-free' and 'progressed-disease' health states (see section 3.17)
- modelling drug acquisition costs per pack and applying every 28 days (see section 3.18).

The committee noted that, even when its preferred assumptions were incorporated into the model, substantial uncertainty remained.

Uncaptured benefits

3.20 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.

Acceptable ICER

3.21 NICE's technology appraisal and highly specialised technologies guidance: the manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per quality-adjusted life year (QALY) 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 3.19). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will take into account other aspects including uncaptured benefits. The committee noted the high level of uncertainty, specifically of:

- the generalisability of PHAROS and IFCT to NHS clinical practice (see section 3.5 and section 3.6)
- the meta-analysis method used to combine PHAROS and IFCT to get an estimate of relative effectiveness (see section 3.8)
- the suitability of the proportional hazards assumption for the IFCT comparison (see section 3.11)
- the unavailability of pooled PHAROS and IFCT Kaplan–Meier data from which to extrapolate longer-term PFS and OS (see section 3.12)
- the modelling of TTD for dabrafenib plus trametinib (see section 3.15).

So, the committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (which is £25,000 to £35,000 per QALY gained).

Equality

3.22 Stakeholders did not raise any equality concerns during the evaluation process, including at draft guidance consultation. The committee considered whether there were any groups that would be disadvantaged by its recommendation. It did not think that any equality issues could be addressed through the technology evaluation.

Conclusion

Recommendation

3.23 Using the committee's preferred assumptions, the cost-effectiveness estimates were within what NICE considers a cost-effective use of NHS resources if it is used as a first-line treatment. So, encorafenib plus binimetinib can be used routinely across the NHS for BRAF V600E mutation-positive advanced NSCLC in adults at first line.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 BRAF V600E mutation-positive advanced non-small-cell lung cancer and the healthcare professional responsible for their care thinks that encorafenib plus binimetinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Chairs

Professor Stephen O'Brien and Dr Richard Nicholas
Chairs, 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 and Leena Issa

Project managers

Ross Dent and Lorna Dunning
Associate directors

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