National Institute for Health and Care Excellence

Health Technology Evaluation

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Pierre Fabre Ltd	Pierre Fabre agrees with the decision to evaluate encorafenib with binimetinib via the single technology appraisal (STA) process.	Thank you for your comment.
Wording	Pierre Fabre Ltd	The wording of the remit is in line with the anticipated marketing authorisation for encorafenib with binimetinib. However, Pierre Fabre requests to update the draft remit to: "…encorafenib with binimetinib within its marketing authorisation for the first line treatment of adults patients with BRAF V600E mutation-positive advanced non-small-cell lung cancer (NSCLC)". As highlighted by the Cancer Drugs Fund (CDF) clinical lead in the NICE appraisal of dabrafenib plus trametinib (TA898) (1), the majority of patients	Thank you for your comment. The scope has been kept broad and in line with the clinical trial at this point. The company can submit modelling and supporting evidence if they consider a sub-

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		with BRAF V600E mutation-positive advanced NSCLC would receive targeted therapy at first line. This was also confirmed by clinical experts during the appraisal, who explained that most of the patients who did not receive dabrafenib plus trametinib at first line would have had other therapies because of genomic testing delays, and that these delays are likely to fall substantially over time. Therefore, the second line-population would fall over time. The committee in TA898 also agreed that the size of the second line population was likely to fall substantially. This was also confirmed to the company by clinical experts during an advisory board held in June 2024, who stated that encorafenib with binimetinib would be offered first line except for circumstances where genomic testing results aren't available. Pierre Fabre therefore considers the relevant population for the appraisal to be untreated BRAF V600E mutation-positive advanced NSCLC (as an alternative option to dabrafenib plus trametinib) Pierre Fabre intends to submit evidence supporting first line positioning only.	population to be more appropriate.
Timing issues	Pierre Fabre Ltd	There is only one other approved targeted therapy treatment option for adult patients with untreated BRAF V600E mutation-positive advanced NSCLC (2), therefore there is high unmet need in this patient population. Pierre Fabre considers the timing of this appraisal to be appropriate.	Thank you for your comment.
Additional comments on the draft remit	Pierre Fabre Ltd	None	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pierre Fabre Ltd	No comments	N/A
Population	Pierre Fabre Ltd	As per the comments on the remit, Pierre Fabre request the population be updated to the first line treatment of adult patients with BRAF V600E mutation-positive advanced NSCLC.	Thank you for your comment. The population has been kept broad and in line with the clinical trial at this point. The company can submit modelling and supporting evidence if they consider a sub-population to be more appropriate.
Subgroups	Pierre Fabre Ltd	As per the comments on the remit, adult patients with BRAF V600E mutation-positive advanced NSCLC would be offered targeted therapy at first line. Patients would receive targeted therapy with either encorafenib with binimetinib or dabrafenib with trametinib regardless of histology of PD-L1 expression. Therefore, these subgroups are not appropriate for this submission.	Thank you for your comment. The subgroups are kept inclusive at this stage to allow the committee to consider any subgroups for which evidence might be identified.
Comparators	Pierre Fabre Ltd	As mentioned above, Pierre Fabre requests the population be updated to the first line treatment of adult patients with BRAF V600E mutation-positive advanced NSCLC. As per the draft scope, the only approved targeted therapy for the treatment of untreated advanced NSCLC with a BRAF V600E mutation is dabrafenib with trametinib. Clinical opinion elicited at the June	Thank you for your comment. The comparators are kept inclusive at this stage to allow the committee to

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		2024 advisory board supports the fact that patients would be offered targeted therapy with dabrafenib with trametinib prior to other treatment options, reserved in second or later lines of therapy. Therefore, Pierre Fabre do not believe the following comparators are relevant to the scope: • *Pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed).* • *Pembrolizumab monotherapy,* • *Atezolizumab monotherapy.*	consider any comparator technologies that are relevant. The population has been kept broad and in line with the clinical trial at this point. The company can submit modelling and supporting evidence if they consider a sub-population to be more appropriate and consider the comparators relevant for that population.
Outcomes	Pierre Fabre Ltd	Pierre Fabre considers the list of outcomes appropriate.	Thank you for your comment.
Equality	Pierre Fabre Ltd	None identified.	Thank you for your comment.
Other considerations	Pierre Fabre Ltd	No comments.	N/A
Questions for consultation	Pierre Fabre Ltd	**Where do you consider encorafenib with binimetinib will fit into the existing care pathway for BRAF V600E positive advanced NSCLC?**	Thank you for your responses to the consultation questions.

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		In line with NICE treatment pathways for NSCLC published in March 2024 (3), and as per clinical expert opinion, encorafenib plus binimetinib is anticipated to be a first-line treatment option for adult patients with BRAF V600E positive NSCLC, regardless of PD-L1 status or histology, in line with positioning for dabrafenib plus trametinib. **What is the standard of care for first-line treatment of BRAF V600E mutation positive advanced NSCLC and what proportion of people receive this treatment?** The only NICE recommended targeted treatment for patients with BRAF V600E mutation positive advanced NSCLC is dabrafenib with trametinib (TA898)(1). As stated above, patients would be offered targeted treatments at first line ahead of immunotherapy or platinum chemotherapy regimens. **Are there any situations where someone would have a chemoimmunotherapy regimen instead of dabrafenib with trametinib as first line treatment of treatment of BRAF V600E mutation positive advanced NSCLC?** As previously stated, the reason patients would not receive targeted therapy at first line would be due to genomic testing delays, which is already low and expected to significantly fall over time. Therefore, situations where patients would have a chemoimmunotherapy regimen instead of dabrafenib with trametinib are increasingly rare. **What is the standard of care for second-line treatment of BRAF V600E mutation positive advanced NSCLC?**	Please see the previous sections for responses to comments on line of therapy and target population.

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		According the NICE guidelines for lung cancer(3), current standard of care for second-line treatment of BRAF V600E mutation positive advanced NSCLC are: For patients with BRAF V600 MT tumours expressing cells with 50% or higher amount of PD-L1: • Pembrolizumab (if PD-L1 above 1%) or • Atezolizumab (any PD-L1 0% to 100%) or • Nivolumab ((any PD-L1 0% to 100%). For patients with tumours expressing cells with less than 50% of PD-L1: • Pembrolizumab (if PD-L1 above 1%) or • Atezolizumab (any PD-L1 0% to 100%) or • Nivolumab (any PD-L1 0% to 100%) or • Docetaxel. **If someone had a BRAF and MEK inhibitor combination at first line, would they be eligible to be retreated with a BRAF and MEK inhibitor combination at second-line? If so, under what circumstances?** BRAF/MEK inhibitors are generally not used as a second-line treatment, if they were administered in first-line, as per clinical expert opinion. This is due to limited clinical trial evidence supporting their sequential use upon disease progression. However, if a patient initially received BRAF/MEK inhibitors for advanced disease and had to discontinue treatment solely due to persistent dose-limiting toxicity, without any documented disease progression, an alternative BRAF/MEK inhibitor regimen may be initiated. In such instances, this would be considered an alternative first-line treatment option.	

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		What is the estimated size of the population with NSCLC who would be eligible for a BRAF and MEK inhibitor combination as a second-line treatment? We do not anticipate the use of BRAF/MEK inhibitiors in a second-line treatment setting since, per the focus of the submission, we anticipate the majority of patients would be/are being treated with targeted therapy at first line. **If retreatment is possible, would there be a preferred order to give the different treatments?** Covered above. **Are the suggested subgroups appropriate?** Covered above. **Are the suggested comparators appropriate?** Covered above. **Would encorafenib with binimetinib be a candidate for managed access?** The preferred funding of encorafenib plus binimetinib for the first line treatment of adult patients with BRAF V600E mutation positive NSCLC is through routine NHS funding via baseline commissioning. However, if the NICE committee feels unable to make a positive recommendation for routine NHS funding, then Pierre Fabre would be open to discussions with NICE and NHS England around potential inclusion in the CDF.	

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		Do you consider that the use of encorafenib with binimetinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? None anticipated. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Not applicable. **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?** There are currently no head-to-head data comparing encorafenib with binimetinib with dabrafenib with trametinib. Therefore, clinical effectiveness will be estimated using an indirect treatment comparison (ITC) using a matching adjusted indirect comparison (MAIC). Preliminary results of the MAIC, using data from the respective pivotal Phase 2 studies for each treatment (PHAROS and BRF113928), suggest that encorafenib with binimetinib maybe associated with a statistically significant benefit in OS and PFS in the first line treatment of adult patients with BRAF V600E mutation positive advanced NSCLC, compared with dabrafenib with trametinib. **Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.** Yes, it is anticipated that encorafenib with binimetinib will be licenced for use in the same position as dabrafenib with trametinib. The most recent change to	

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		the treatment pathway for BRAF V600E mutation positive advanced NSCLC was the approval of dabrafenib with trametinib as a first line therapy (TA898)(3). **Will the intervention be used to treat the same population as the comparator(s)?** Yes, it is anticipated that encorafenib with binimetinib will be licenced for use in the same population as dabrafenib with trametinib. **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** As noted above, preliminary results may suggest a statistically significant benefit for encorafenib with binimetinib in OS and PFS compared with dabrafenib with trametinib. **Would it be appropriate to use the cost-comparison methodology for this topic?** As noted above, preliminary results may suggest a statistically significant benefit for encorafenib with binimetinib in OS and PFS compared with dabrafenib with trametinib. Pierre Fabre plan to submit via the single technology appraisal (STA) process using cost-utility methods, but would be open to discussion regarding cost comparison methodology only if the NICE appraisal team felt this was appropriate based on the current value propositions of both treatments (i.e. both from a clinical and cost perspective)	

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Additional comments on the draft scope	Pierre Fabre Ltd	None	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Roy Castle Lung Cancer Foundation
Novartis UK
British Thoracic Oncology Group (BTOG)