National Institute for Health and Care Excellence

Health Technology Evaluation

Dabrafenib in combination with trametinib for treating advanced, metastatic BRAF V600E mutation-positive non-small-cell lung cancer (review of technology appraisal 564) [ID3851]

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
Wording	Company (Novartis)	No. The remit of the appraisal should be aligned with the marketing authorisation and therefore should be changed to: *"To appraise the clinical and cost effectiveness of dabrafenib in combination with trametinib within its marketing authorisation for treating advanced, metastatic BRAFV600 mutation-positive non-small-cell lung cancer." Electronic Medicines Compendium. Dabrafenib & Trametinib, Updated 21st April 2022.* *Accessed at* Tafinlar 50 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) & Mekinist 0.5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Scope amended to reflect MA (V600 instead of V600E)

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Company (Novartis)	As part of NHS England's interim treatment options during COVID-19 pandemic policy, dabrafenib in combination with trametinib is currently available for BRAF positive metastatic disease as an oral alternative to intravenous chemotherapy to reduce risk of immunosuppression and make better use of clinical capacity. As the COVID-19 pandemic policy is temporary, the proposed timelines for submission and evaluation are appropriate given the unmet need for a targeted treatment option for patients with NSCLC harbouring a BRAF mutation. **Accessed at NG161 NHS England interim treatment options during the COVID 19 pandemic (nice.org.uk) Updated 1st April 2022**	No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company (Novartis)	The background section is accurate, however for completeness, Novartis would like to point out that the background section does not acknowledge the recent transition to Genomic Hubs, where next-generation sequencing testing panels are being applied to improve the diagnostic testing process. Currently, the National Genomic Testing Directory for Cancer recommend the NHS test for BRAF mutations alongside other oncogenic driver mutations such as EGFR, ALK, KRAS, and MET for patients with NSCLC.[1] This will allow clinicians to use targeted therapies, such as dabrafenib with	No action taken. The background section aims to give a brief overview including the background of the disease, its epidemiology and treatment pathways. Diagnostic test costs are discussed below.

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		trametinib, as a first-line treatment option in a similar way to other specific NICE treatment pathways for cancers which have EGFR, ALK, ROS-1 or KRAS gene mutations.	
Population	Company (Novartis)	See comment in the remit section. The population should be amended to be aligned with the marketing authorisation (i.e., BRAFV600) for consistency.	Population updated to reflect MA.
Subgroups	Company (Novartis)	n/a	n/a
	Comparator company (Pierre Fabre)	We would like to highlight that due to the small patient numbers for the indication under consideration evaluation of specific subgroups will reduce the patient pool further while increasing the level of uncertainty associated with any results. On this basis we do not consider it appropriate to consider at the subgroups specified.	No changes made. Whilst smaller sample sizes often associated with subgroups may increase uncertainty in effect estimates, the scope is clear that subgroups will be considered “if the evidence allows” and any associated uncertainty would be taken into account during the appraisal.
Comparators	Company (Novartis)	Novartis acknowledge the comparator section accurately reflects full range of possible treatment options available for metastatic non-small-cell lung cancer (NSCLC) patients based on whether patients are untreated or previously treated, histology, and programmed death-ligand 1 (PD-L1) status. Novartis consider that immunotherapy and/or chemotherapy are likely to be the main comparators for dabrafenib in combination with trametinib.	Removed atezolizumab plus bevacizumab, carboplatin and paclitaxel from comparator list.

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		Further, we do not believe atezolizumab plus bevacizumab, carboplatin and paclitaxel is a relevant comparator in those patients who previously failed prior EGFR or ALK directed therapy (TA584). The expression of a BRAF mutation and other oncogenic driver mutations (such as EGFR, ROS1, or ALK1) are generally mutually exclusive, implying TA584 has little relevance to this appraisal.[2]	
Outcomes	Company (Novartis)	No comment.	No action required
Economic Analysis	Company (Novartis)	Since diagnostic testing has transitioned to the Genomic Hubs recently, local costs of testing for BRAF will not be included in the economic model. The recent NHS England's National Genomics Testing Directory for cancer includes BRAF testing for NSCLC, so the cost of testing for BRAF mutation was considered a cost which would be common to all patients.[1]	No changes made. Whilst the National Genomics Testing directory does recommend testing for BRAF and other oncogenic drivers, it is unclear to what extent this is carried out in clinical practice. Section 4.8.1 of the NICE HTE manual states that if a diagnostic test is not routinely used in the NHS but is introduced to support the treatment decision for the technology, the associated costs should be included. This will be discussed in the appraisal but including sensitivity analyses with and without these costs may be useful.

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Equality	Company (Novartis)	None.	n/a
Other considerations	Company (Novartis)	According to NICE clinical guidelines (NG122), lung cancer patients with a sensitising mutation should receive a targeted agent as a first-line therapy.[3] This is further supported by international guidelines such as European Society of Medical Oncology (ESMO).[2] As noted above, the BRAF mutation is currently listed on the National Genomics Testing Directory for cancer as a mutation that should be tested for alongside other oncogenic driver mutations.[1] Therefore, BRAF is an actionable mutation, and a NICE specific treatment pathway should be considered in-line with other actionable oncogenic driver mutations in patients with NSCLC.	No changes made. This will be discussed at appraisal.
Innovation	Company (Novartis)	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, dabrafenib with trametinib is currently the only licensed treatment available for patients with NSCLC harbouring a BRAF mutation. This treatment is currently available via the interim COVID-19 pandemic policy, and several patients have been treated to date. Now that the National Testing Directory for Cancer include BRAF as part of a panel to test for oncogenic driver mutations in	No changes made. The company may include a case for the innovative nature of this technology in the submission. This will be discussed during the appraisal as noted in section 6.2.34 of the NICE HTE manual.

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		patients with NSCLC, the combination of dabrafenib and trametinib may provide a step-change in the management of the condition by creating a BRAF V600 positive treatment pathway in a similar manner to existing NICE specific pathways for EGFR, ALK, ROS-1 or KRAS gene mutations as described in the background section. Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Not applicable.**	
Questions for consultation	Company (Novartis)	Where do you consider dabrafenib in combination with trametinib will fit into the existing care pathway for advanced non-small-cell lung cancer with BRAF V600E mutation? In-line with NICE specific treatment pathways for EGFR, ALK, ROS-1 or KRAS gene mutations we anticipate patients harbouring a BRAF mutation will have the opportunity to receive a targeted therapy as a treatment option in first- or second-line. Which treatments are considered to be established clinical practice in the NHS for advanced non-small-cell lung cancer with BRAF V600E mutation? See comparator section.	No action needed

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		Have all relevant comparators for dabrafenib in combination with trametinib been included in scope: focus is on whether untreated or treated, squamous or non-squamous, and taking into account PD-L1 status. Would any of the targeted molecules (e.g. alectinib, tepotinib, selpercatinib) be used to treat the population in scope? See comparator section. Can advanced non-small-cell lung cancer which is positive for the BRAF V600E mutation also be positive for other biomarkers (e.g. EGFR, ALK, ROS-1, RET fusion)? If yes, how would this impact clinical management? BRAF expression alongside other actionable mutations in patients with NSCLC is generally considered to be mutually exclusive.[2] Are there any other subgroups of people in whom dabrafenib in combination with trametinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No. Would dabrafenib in combination with trametinib be a candidate for managed access?	

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		It is envisioned that a managed access agreement would not be required as the submission will be underpinned by the pivotal trial that has now reported 5-year follow-up data. Furthermore, comparative effectiveness to other treatments will be assessed and presented as part of this appraisal which Novartis believe should address any remaining clinical uncertainty. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which dabrafenib in combination with trametinib is licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;	

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		• could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. **No comment.**	
Additional comments on the draft scope	Company (Novartis)	No comments.	No action required

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

Comparator company: Roche