NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SIngle Technology Appraisal

Dabrafenib in combination with trametinib for treating advanced, metastatic BRAF V600E mutation-positive non-small-cell lung cancer [ID3851]

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of dabrafenib in combination with trametinib within its marketing authorisation for treating advanced, metastatic BRAF V600E mutation-positive non-small-cell lung cancer.

Background

Lung cancer falls into 2 main histological categories: around 80–85% are non-small-cell lung cancers (NSCLC) and the remainder are small cell lung cancers.[1] NSCLC can be further classified into 3 main histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma.[1] Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage 3) or to other parts of the body (metastatic disease; stage 4). BRAF is a protein which is part of the mitogen activated protein kinase signalling pathway, which helps to regulate cell proliferation, differentiation and death.[2]

In 2020 around 28,300 cases of non-small-cell lung cancer were diagnosed in England.[3] In the same year 19% of all lung cancer cases were stage 3 and 40% were stage 4.[3] Lung cancer survival rates are relatively low, between 2013 and 2017 40% of people with lung cancer survived for one year and 16% survived for 5 years or longer. BRAF mutations are found in approximately 1-4% of NSCLCs, and of these mutations about 50% are BRAF V600E mutations.[4]

Current clinical management for advanced or metastatic (stage 3 or 4) NSCLC typically aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes surgery, chemotherapy, radiotherapy, chemoradiation or targeted small molecule and immunotherapy drugs. Treatment choices are influenced by the histology of the condition (squamous, or non-squamous) and by previous treatments. Choices are also influenced by the presence of certain biomarkers such as the programmed cell death-ligand 1 (PD-L1) or mutations affecting proteins such as epidermal growth factor receptor (EGFR), anaplastic-lymphoma kinase (ALK) or the ROS-1 and KRAS receptors. There are specific NICE treatment pathways for cancers which have EGFR, ALK, ROS-1 or KRAS gene mutations but not currently for BRAF mutations.

Disease with no biomarkers

For untreated non-squamous metastatic NSCLC with no ALK or EGFR mutations, pembrolizumab with pemetrexed and platinum chemotherapy is recommended (TA683). Pemetrexed is also recommended as maintenance therapy for non-squamous NSCLC which is locally advanced or metastatic and which has not progressed after other chemotherapies (TA190 & TA402). For those who have

adenocarcinoma or large cell carcinoma (subsets of non-squamous NSCLC) pemetrexed is recommended as first line chemotherapy (TA181) and nintedanib with docetaxel is recommended for adenocarcinoma that has progressed after first line chemotherapy (TA347).

For those with locally advanced or metastatic NSCLC who have previously had chemotherapy (or targeted EGFR or ALK treatment) atezolizumab is recommended (TA520). For those who have squamous NSCLC which is locally advanced or metastatic and which has been previously treated with chemotherapy, nivolumab is recommended (TA655).

Disease with PD-L1 biomarker

For those with untreated metastatic NSCLC disease with no EGFR or ALK mutations, where tumour PD-L1 expression is 50% or more, NICE recommends pembrolizumab monotherapy (TA531) or atezolizumab monotherapy [which can also be given if 10% or more of tumour infiltrating immune cells express PD-L1] (TA705). For untreated metastatic NSCLC where targeted EGFR or ALK therapy has failed and which has tumour PD-L1 expression of 0 to 49%, atezolizumab with bevacizumab, carboplatin and paclitaxel is recommended (TA584). For untreated metastatic squamous NSCLC which expresses PD-L1 on 0 to 49% of cells (or 50% or more if urgent treatment is required) pembrolizumab with carboplatin and paclitaxel is recommended (TA770).

For those who have locally advanced or metastatic NSCLC whose tumours express PD-L1 on 1% or more of cells and which have been previously treated with chemotherapy, NICE recommends pembrolizumab [also given after treatment with an EGFR or ALK inhibitor if appropriate] (TA428) and nivolumab when the NSCLC is non-squamous (TA713).

The technology

Dabrafenib (Tafinlar®, Novartis Pharmaceuticals) is a selective inhibitor of BRAF V600E kinase activity. Trametinib (Mekinist®, Novartis pharmaceuticals) is an inhibitor of MEK1 and MEK2 activity. BRAF V600E and MEK proteins work in a chain to send signals to encourage cell growth, by blocking these proteins these drugs cause cancer cells to stop growing and die. Both treatments are administered orally.

Dabrefanib with trametinib is indicated for the treatment of adult patients with advanced non-small-cell lung cancer with a BRAF V600E mutation.

Intervention(s)	Dabrafenib with trametinib
Population(s)	Adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation
Subgroups	If the evidence allows the following subgroups will be considered: • previous therapy (treated or untreated) • tumour histology (squamous or non-squamous)

	• Level of PD-L1 expression (strong positive or weak positive)
Comparators	**Untreated NSCLC disease:** For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Atezolizumab monotherapy (Tumour PD-L1 expression of 50% or more or of 10% or more on tumour infiltrating immune cells) • Pembrolizumab combination with pemetrexed and platinum chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (only if urgent clinical intervention is needed) For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel **For previously treated disease:**

	For people with non-squamous NSCLC PD-L1 ≥50%: • Platinum doublet • Pemetrexed • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care For people with non-squamous NSCLC PD-L1 <50%: • Atezolizumab monotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel (only after initial EGFR or ALK targeted treatment has failed) • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care For people with non-squamous NSCLC which is PD-L1 1% or more: • Pembrolizumab monotherapy • Nivolumab monotherapy For people with squamous NSCLC PD-L1 >50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Best supportive care For people with squamous NSCLC PD-L1 <50%: • Atezolizumab monotherapy • Docetaxel • Best supportive care For people with squamous NSCLC which is PD-L1 1% or more*: • Pembrolizumab monotherapy • Nivolumab (* no PD-L1 status requirement)
Outcomes	The outcome measures to be considered include: • overall survival

	• progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the interventions, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The use of dabrafenib in combination with trametinib is conditional on the presence of the BRAF V600E that the test detects]. The economic modelling should include the costs associated with diagnostic testing for [biomarker] in people with [the disease] who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals:** Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (2022) NICE technology appraisal guidance 770. Review date 2025 Nivolumab with ipilimumab and chemotherapy for untreated metastatic **non-small-cell** lung cancer (2021) NICE technology appraisal guidance 724. Review date 2024

	Nivolumab for advanced **non**-squamous **non-small-cell** lung cancer after chemotherapy (2021) NICE technology guidance 713 Review date 2024 Atezolizumab monotherapy for untreated advanced **non-small-cell** lung cancer (2021) NICE technology guidance 705 Review date 2024 Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, **non**-squamous **non-small-cell** lung cancer (2021) NICE technology guidance 683 Review date 2024 Nivolumab for advanced squamous **non-small-cell** lung cancer after chemotherapy (2020) NICE technology guidance 655 Review date 2023 Atezolizumab in combination for treating metastatic **non**-squamous **non-small-cell** lung cancer (2019) NICE technology guidance 584 Review date 2022 Pembrolizumab for untreated PD-L1-positive metastatic **non-small-cell** lung cancer (2018) NICE technology guidance 531 Review date 2021 Atezolizumab for treating locally advanced or metastatic **non-small-cell** lung cancer after chemotherapy (2018) NICE technology guidance 520 Review date 2021 Pembrolizumab for treating PD-L1-positive **non-small-cell** lung cancer after chemotherapy (2017) NICE technology guidance 428 Review date 2021 Pemetrexed for the maintenance treatment of **non-small-cell** lung cancer (2010) NICE technology guidance 190 Review date to be confirmed Necitumumab for untreated advanced or metastatic squamous **non-small-cell** lung cancer (2016, reviewed 2020) NICE technology guidance 411 Review date to be confirmed Pemetrexed maintenance treatment for **non**-squamous **non-small-cell** lung cancer after pemetrexed and cisplatin (2016) NICE technology guidance 402 Review date 2019 Ramucirumab for previously treated locally advanced or metastatic **non-small-cell** lung cancer (2016, reviewed 2019) NICE technology guidance 403 Review date to be confirmed Nintedanib for previously treated locally advanced, metastatic, or locally recurrent **non-small-cell** lung cancer (2015) NICE technology guidance 347 Erlotinib monotherapy for maintenance treatment of **non-small-cell** lung cancer (2011) NICE technology guidance 227 Pemetrexed for the first-line treatment of **non-small-cell** lung cancer (2009) NICE technology guidance 181

	Pemetrexed for the treatment of **non-small-cell** lung cancer (2007) NICE technology guidance 124 **Related appraisals in development (including suspended appraisals)** Atezolizumab with carboplatin or cisplatin and pemetrexed for untreated advanced non-squamous non-small-cell lung cancer NICE technology appraisal guidance [ID1495] Publication date to be confirmed. Avelumab for untreated PD-L1 positive non-small-cell lung cancer. NICE technology appraisal guidance [ID1261]. Publication date to be confirmed. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations. NICE technology appraisal guidance [ID1143]. Suspended. Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer. NICE technology appraisal guidance [ID1187]. Suspended. Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small-cell lung cancer. NICE technology appraisal guidance [ID1135]. Suspended. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer NICE technology guidance [ID1566] Expected publication date June 2021 Nivolumab monotherapy for non-small-cell lung cancer. NICE technology appraisal guidance [ID1088]. Suspended. Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score. NICE technology appraisal guidance [ID1247]. Suspended. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer. NICE technology appraisal guidance [ID1277]. Publication date to be confirmed. **Related Guidelines:** EGFR-TK mutation testing in adults with locally advanced or metastatic **non-small-cell** lung cancer (2013). NICE diagnostic guideline 9. Lung cancer: diagnosis and management (2019) NICE guideline 122 **Related Interventional Procedures:** Microwave ablation for primary or metastatic cancer in the lung (2022) Interventional procedures guidance 716. Review date 2025

	Irreversible electroporation for treating primary lung cancer and metastases in the lung (2013) Interventional procedures guidance 441. Review date to be confirmed **Related Quality Standards:** Lung cancer in adults (2012). NICE quality standard 17
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health, NHS Outcomes Framework 2016-2017 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4, 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 **Other policies** Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020

Questions for consultation

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?

Which treatments are considered to be established clinical practice in the NHS for advanced non-small-cell lung cancer with BRAF V600E mutation?

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?

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?

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?

Would dabrafenib in combination with trametinib be a candidate for managed access?

Do you consider dabrafenib in combination with trametinib 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)?

Do you consider that the use of dabrafenib in combination with trametinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

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;

- 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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. Cancer Research UK (2020) Types of lung cancer. Accessed April 2022

2. Chan, X. Y. et al (2017) Role Played by Signalling Pathways in Overcoming BRAF Inhibitor Resistance in Melanoma

3. National Lung Cancer Audit (2022) Annual Report (2019/2020 data) Accessed April 2022

4. Shiau, C.J. Tsao, M. -S. 2017. Diagnostic Molecular Pathology. Chapter 23: Molecular testing in lung cancer Accessed April 2022