NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# April 2023

# Encorafenib with binimetinib for treating metastatic BRAF V600 mutant non-small-cell lung cancer

| Company/Developer | Pierre Fabre Ltd |
|---|---|

☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 33752 | NICE TSID: 11873 | UKPS ID: 662211, 663811 |
|---|---|---|

## Licensing and Market Availability Plans

Currently in phase II clinical trials.

## Summary


Encorafenib in combination with binimetinib is in development for the treatment of BRAF V600E mutant metastatic non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Metastatic cancer means it has spread around the body from where it started in the lungs. The *BRAF* gene encodes for a protein (called BRAF) which is involved in stimulating cell division. A common mutation to this gene is 'V600E'. This abnormal form of BRAF plays a role in the development of the cancer by allowing uncontrolled division of the tumour cells. There is currently no recommended treatment options for this specific mutation in NSCLC, highlighting the need for a therapy.

Encorafenib in combination with binimetinib has shown antitumor activity. It can be administered orally to block the action of the abnormal BRAF to slow down the growth and spread of the cancer. In tumours with a BRAF V600 mutation, an abnormal form of the protein BRAF is present, which switches on another protein called MEK involved in stimulating cell division. This encourages cancers to develop by allowing uncontrolled division of cells. The active substance in Braftovi, encorafenib, works by blocking the BRAF protein thereby stopping its activation of cell division and slowing down the growth and spread of the cancer. If licensed, encorafenib in combination with binimetinib will offer a novel treatment option for adults with BRAF mutation V600E NSCLC.

## Proposed Indication

Encorafenib in combination with binimetinib for the treatment of adult patients with metastatic BRAF V600E-mutant non-small cell lung cancer (NSCLC).[1,2]

## Technology

### Description

Encorafenib (Braftovi) is a potent and highly selective adenosine triphosphate (ATP)-competitive small molecule rapidly accelerated fibrosarcoma (RAF) kinase inhibitor. Encorafenib suppresses the RAF/ mitogen-activated extracellular signal regulated kinase (MEK)/ extracellular signal-related kinase (ERK) pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K).[3] It inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically BRAF kinase, thereby inhibiting BRAF V600 mutation-positive cell growth.[4]

Binimetinib (Mektovi) is an adenosine triphosphate (ATP)-uncompetitive, reversible inhibitor of the kinase activity of MEK1 and MEK2. MEK proteins are upstream regulators of the ERK pathway, which promotes cellular proliferation. This pathway is often activated by mutated forms of BRAF which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.[5] Encorafenib and binimetinib both inhibit the MAPK pathway, resulting in higher anti-tumour activity.[3,5]

Encorafenib in combination with binimetinib is currently in phase II clinical trials (NCT03915951, NCT04526782) for the treatment of BRAF V600E mutant NSCLC. [1,2] Patients will receive the following via oral administration: 450mg of encorafenib (6 × 75 mg capsule) once daily and 45mg of binimetinib (3x15mg tablet) twice daily.[1,2]

### Key Innovation

Targeting two kinases within the same RAS/RAF/MEK/ERK pathway achieves greater antitumor activity and prolongs progression-free survival (PFS). In BRAF V600E mutant NSCLC, combined BRAF/MEK inhibition is associated with better response rates and PFS compared with BRAF inhibitor monotherapy.[6-9] If licensed, encorafenib in combination with binimetinib will offer a novel treatment option for BRAF V600E mutant NSCLC.

### Regulatory & Development Status

Binimetinib in combination with encorafenib currently has Marketing Authorisation in the EU/UK for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[5] Encorafenib currently has Marketing Authorisation in the EU/UK in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy. Encorafenib in combination with binimetinib also has Marketing Authorisation in the EU/UK for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[3,5]

Encorafenib in combination with binimetinib is currently in phase III clinical development for:[10]

- High risk stage 2 melanoma with a BRAF mutation
- Advanced or metastatic melanoma
- Metastatic colorectal cancer with a BRAF V600E mutation

## Patient Group

### Disease Area and Clinical Need

There are two main types of primary lung cancer: NSCLC and small cell lung cancer (SCLC). NSCLC is the most common lung cancer. The three main types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[11] Some people with NSCLC have a mutation in the BRAF gene, of which a common mutation is called BRAF V600. Symptoms of lung cancer can include a persistent cough, repeated or extended chest infections, feeling breathless or wheezy, coughing up blood, and persistent chest or shoulder pain.[12] Several things can increase the risk factor of developing lung cancer such as a history of smoking, age, exposure to certain chemicals or pollution, lowered immunity, previous history of cancer, or a family history of lung cancer.[13]

There are around 48,500 new lung cancer cases in the UK annually. Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016-2018). Around 80 to 85 out of 100 lung cancers (around 80 - 85%) in the UK are NSCLC.[14] BRAF mutations are rare in NSCLC, occurring in 1–5% of cases.[15] In 2020/21 there were 86,043 hospital admissions with a primary diagnosis of malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[16] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV (metastatic) disease was 19.3% at one year and 2.9% at five years.[17]

### Recommended Treatment Options

There are currently no approved pharmacological treatment options for this indication/patient population Patients with stage IV NSCLC with BRAF V600 mutation should be exposed in first or second line to BRAF/MEK inhibition using dabrafenib/trametinib. If patients have received BRAF/MEK inhibition in the first-line setting, then they may be offered platinum-based ChT in the second line setting.[18]

| Clinical Trial Information | | |
|---|---|---|
| Trial | **PHAROS; NCT03915951, EudraCT 2019-000417-37**; A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer<br>**Phase II** – Active, not recruiting<br>**Location(s):** 3 EU countries, USA, and Republic of Korea<br>**Study Completion Date:** June 2024 | **ENCO-BRAF; NCT04526782;** A Phase II Study of the BRAF Inhibitor Encorafenib in Combination With the MEK Inhibitor Binimetinib in Patients With BRAFV600E-mutant Metastatic Non-small Cell Lung Cancer<br>**Phase II –** Recruiting<br>**Location(s):** France<br>**Study Completion Date:** March 2026 |
| Trial Design | Non-randomised, single group assignment, open label | Non-randomised, parallel assignment, open label |
| Population | N=98; aged 18 years and over; subjects with histologically confirmed diagnosis of NSCLC that is currently Stage IV, and presence of a BRAFV600E mutation. | N=119; aged 18 years and over; subjects with histologically confirmed diagnosis of NSCLC that is currently Stage IV, and presence of a BRAFV600E mutation. |

| | | |
|---|---|---|
| Intervention(s) | Encorafenib: (oral) self-administered 450 mg (6 × 75 mg capsule) once daily.<br>Binimetinib: (oral) self-administered 45 mg (3 × 15 mg tablet) twice daily. | Encorafenib: (oral) self-administered 450mg (6 × 75 mg capsule) once daily.<br><br>Binimetinib: (oral) self-administered 45 mg (3 × 15 mg tablet) twice daily. |
| Comparator(s) | No comparator used | No comparator used |
| Outcome(s) | Primary outcome measure:<br>• Objective response rate [time frame: up to 24 months]<br>See trial record for full list of other outcomes | Primary outcome measure:<br>• Objective response rate [time frame: 6 months]<br>See trial record for full list of other outcomes |
| Results (efficacy) | - | - |
| Results (safety) | - | - |

## Estimated Cost

Encorafenib is already marketed in the UK for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation (in combination with binimetinib) and metastatic colorectal cancer with a BRAF V600E mutation (in combination with cetuximab); a pack of 28 x 75mg tablets costs £1,400, and treatment with 6x75mg each day on a 28-day cycle would cost £8,400. [19] Binimetinib is already marketed in the UK for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation. A pack of 84 x 15mg tablets costs £2,240, and treatment with 3x15mg each day on a 28-day cycle would cost £2,240. [20]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Dabrafenib with trametinib for treating advanced BRAF V600E mutation-positive non-small-cell lung cancer (ID3851). Expected May 2023.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). Updated December 2019.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a

### Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2. 2021.[21]
- European Society for Medical Oncology (ESMO). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2019.[22]
- European Society for Medical Oncology (ESMO). ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[23]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[24]

## Additional Information

## References


1 ClinicalTrials.gov. *An Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer. Trial ID: NCT03915951*. April 16, 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03915951?term=NCT03915951&draw=2&rank=1 [Accessed 21st February 2023].

2 ClinicalTrials.gov. *ENCOrafenib With Binimetinib in bRAF NSCLC (ENCO-BRAF). Trial ID: NCT04526782*. 2020. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04526782?term=NCT04526782&draw=2&rank=1 [Accessed 23rd February 2023].

3 Electronic Medicines Compendium (EMC). *Braftovi 50 mg hard capsules*. 2022. Available from: https://www.medicines.org.uk/emc/product/9499/smpc#PHARMACODYNAMIC_PROPS [Accessed 23rd February 2023].

4 National Institute for Health and Care Excellence (NICE). *Encorafenib*. 2023. Available from: https://bnf.nice.org.uk/drugs/encorafenib/#drug-action [Accessed 23rd February 2023].

5 Electronic Medicines Compendium (EMC). *Mektovi 15 mg film-coated tablets*. 2021. Available from: https://www.medicines.org.uk/emc/product/9501#PHARMACODYNAMIC_PROPS [Accessed 23rd February 2023].

6 O'Leary CG, Andelkovic V, Ladwa R, Pavlakis N, Zhou C, Hirsch F, et al. Targeting BRAF mutations in non-small cell lung cancer. *Transl Lung Cancer Res*. 2019;8(6):1119-24. Available from: https://doi.org/10.21037/tlcr.2019.10.22.

7 Roviello G, D'Angelo A, Sirico M, Pittacolo M, Conter FU, Sobhani N. Advances in anti-BRAF therapies for lung cancer. *Investigational New Drugs*. 2021;39(3):879-90. Available from: https://doi.org/10.1007/s10637-021-01068-8.

8 Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations. *New England Journal of Medicine*. 2012;367(18):1694-703. Available from: https://doi.org/10.1056/NEJMoa1210093.

9 Menzer C, Menzies AM, Carlino MS, Reijers I, Groen EJ, Eigentler T, et al. Targeted Therapy in Advanced Melanoma With Rare BRAF Mutations. *Journal of Clinical Oncology*. 2019;37(33):3142-51. Available from: https://doi.org/10.1200/JCO.19.00489.

10 ClinicalTrials.gov. *Search for: encorafenib with binimetinib*. Status: Recruiting, Not yet recruiting, active, not recruiting, completed, enrolling by invitation Studies | Phase 2, 3. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=encorafenib+with+binimetinib&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort [Accessed 23rd February 2023].

11 Macmillan Cancer Support. *Non-small cell lung cancer (NSCLC)*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/non-small-cell-lung-cancer [Accessed 23rd February 2023].

12 Macmillan Cancer Support. *Signs and symptoms of lung cancer*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/signs-and-symptoms-of-lung-cancer [Accessed 16th March 2023].
13 Macmillan Cancer Support. *Causes and risk factors of lung cancer*. 2020. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/causes-and-risk-factors-of-lung-cancer [Accessed 16th March 2023].
14 Cancer Research UK. *Lung cancer statistics*. 2023. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 23rd February 2023].
15 O'Leary CG, Andelkovic V, Ladwa R, Pavlakis N, Zhou C, Hirsch F, et al. Targeting BRAF mutations in non-small cell lung cancer. *Translational Lung Cancer Research*. 2019;8(6):1119-24. https://tlcr.amegroups.com/article/view/33640.
16 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 23rd Febraury 2023].
17 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed .
18 European Society for Medical Oncology (ESMO). *Lung & Chest Cancers Pocket Guideline 2022*. Available from: http://interactiveguidelines.esmo.org/esmo-web-app/toc/index.php?subjectAreaID=1&loadPdf=1 [Accessed 16th March 2023].
19 National Institute for Health and Care Excellence (NICE). *Encorafenib -Medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/encorafenib/medicinal-forms/ [Accessed 23rd Febraury 2023].
20 National Institute for Health and Care Excellence (NICE). *Binimetinib - medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/binimetinib/medicinal-forms/ [Accessed 23rd February 2023].
21 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2021;19(3):254-66. Available from: https://doi.org/10.6004/jnccn.2021.0013.
22 European Society for Medical Oncology (ESMO). *ESMO Clinical Practice Guidelines: Lung and Chest Tumours*. 2023. Available from: https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours [Accessed 23rd February 2023].
23 Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Annals of Oncology*. 2014;25(8):1475-84. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2934808-2.
24 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer*. Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 23rd February 2023].

***NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***