Health Technology Briefing
August 2022

Encorafenib with binimetinib for treating metastatic BRAF V600E mutant non-small-cell lung cancer

Company/Developer	Pierre Fabre Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27563	NICE ID: 11786	UKPS ID: 663809, 662497

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 non-small-cell lung cancer (NSCLC). The BRAF gene encodes for a protein, also called BRAF, a protein involved in stimulating cell division. A common mutation to this gene is 'V600'. This abnormal form of BRAF plays a role in the development of the cancer by allowing uncontrolled division of the tumour cells. Blocking the action of the abnormal BRAF helps to slow down the growth and spread of the cancer. There is currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for this specific indication, highlighting the need for a therapy.

Encorafenib in combination with binimetinib has shown antitumour activity. It can be administered orally to block the action of the abnormal BRAF to slow down the growth and spread of the cancer. The targeted therapy drug combination of this treatment helps address the BRAF mutation (encorafenib) and the MEK protein (binimetinib). If licensed, encorafenib in combination with binimetinib will offer a novel treatment option for adults with BRAF mutation V600E NSCLC.

Proposed Indication

Treatment of metastatic BRAF V600E mutated 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 non-small-cell lung cancer (NSCLC).[1,2] Patients will receive the following via oral administration: 450 mg of encorafenib (6 × 75 mg capsule) once daily (QD) and 45mg of binimetinib (3 × 15 mg tablet) twice daily (BID) based on the clinical trial regimen.[1,2]

Key Innovation

BRAF is part of the MAPK pathway, which controls cell growth and proliferation. Activating BRAF mutations act as oncogenic drivers by causing constitutive activation of downstream MAPK pathway signalling, resulting in unchecked cell growth and proliferation. In targeting BRAF-mutant cancers, BRAF inhibitors are typically used in combination with inhibitors of the downstream kinase MEK. Targeting two kinases within the same RAS/RAF/MEK/ERK pathway achieves a greater antitumour 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] If licensed, encorafenib in combination with binimetinib will offer a novel treatment option for BRAF V600 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] Furthermore, encorafenib currently has Marketing Authorisation in the EU/UK in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.[3]

Encorafenib in combination with binimetinib is currently in phase III clinical development for:[7]

- Melanoma
- Pancreatic carcinoma
- Hairy cell leukaemia

- Thyroid cancer
- Colorectal cancer
- Solid tumours
- Advanced BRAF mutant cancers
- Multiple myeloma
- High grade glioma

Patient Group

Disease Area and Clinical Need

There are two main types of primary lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common lung cancer.[8] The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[9] Some people with NSCLC have changes in a gene called BRAF (known as 'gene mutations'). One common BRAF mutation is called 'V600'. Combinations of medicines that block proteins encoded by mutant BRAF and another gene called MEK can shrink tumours and slow their progression.[6]

There are around 48,500 new lung cancer cases in the UK annually. Lung cancer is the 3rd 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.[10] BRAF mutations are rare in NSCLC, occurring in 1–5% of cases.[11] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[12] 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.[13]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for this patient group. 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.[14]

Clinical Trial Information

Trial	NCT03915951; A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer **Phase II:** Active, not recruiting **Location(s):** 3 EU countries and US **Primary completion date:** March 2023
Trial Design	Single group assignment, open label
Population	N = 97; ages 18 years and older; histologically confirmed diagnosis of NSCLC that is currently Stage IV; presence of a BRAFV600E mutation in lung cancer tissue as determined by a local laboratory assay or the presence of other BRAFV600 mutations other than V600E (i.e. K or D) will be considered; patients who are either treatment-naïve OR who have received 1) first-line platinum-based chemotherapy OR 2) first-line treatment with an anti-programmed cell

	death protein 1 (PD-1)/ programmed cell death protein ligand 1(PD-L1) inhibitor given alone or in combination with platinum-based chemotherapy
Intervention(s)	Study treatment with encorafenib and binimetinib will be self-administered orally without regard to food. Patients will receive the following per 28-day (± 3 days) cycle: • Encorafenib: 450 mg (6 × 75 mg capsule) once daily (QD) • Binimetinib: 45 mg (3 × 15 mg tablet) twice daily (BID)
Comparator(s)	N/A
Outcome(s)	Primary outcome(s): Objective Response Rate (ORR) as Determined by Independent Radiology Review (IRR) per RECIST v1.1 in the Treatment Naïve and Previously Treated Settings [time frame: up to 24 months] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	**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 **Phase II:** Recruiting **Location(s):** France **Primary completion date:** February 2024
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 119; ages 18 years and older; histologically confirmed diagnosis of NSCLC that is currently Stage IV; presence of a BRAFV600E mutation in lung cancer tissue; patients i) (COHORT A) who are either treatment-naïve (e.g., no prior systemic therapy for advanced/metastatic disease), ii) (COHORT B) who have received 1) first-line platinum-based chemotherapy OR 2) first-line treatment with an anti-PD-1/L-1 inhibitor given alone or in combination with platinum-based chemotherapy or in combination with immunotherapy with or without platinum-based chemotherapy
Intervention(s)	Encorafenib: 450 mg (6 × 75 mg capsule) QD Binimetinib: 45 mg (3 × 15 mg tablet) BID
Comparator(s)	N/A
Outcome(s)	Primary outcome(s): • Objective response rate [time frame: 6 months] - objective Response Rate at 6 months using RECIST1.1 criteria See trial record for full list of outcomes

Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost per pack (28 capsules) of 50mg and 75mg (42 capsules) of encorafenib is £622.22 and £1,400.00 respectively.[15]
The estimated cost per pack (84 tablets) of 15mg of binimetinib is £2,240.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer (ID3851). Expected date of issue 05 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.[17]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[18]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[19]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[20]
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Additional Information

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