Encorafenib (Braftovi®) in combination with binimetinib (Mektovi®) for the treatment of advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]

Encorafenib (Braftovi®) is an oral, selective, reversible small-molecule RAF kinase inhibitor, with a long dissociation half-life of >30 hours. Binimetinib (Mektovi®) is an oral, ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2 activation.

Indication [2, 3]

Encorafenib (Braftovi®) in combination with binimetinib (Mektovi®) is indicated for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation.

Incidence

- In Austria, in 2022, a total of 5,203 patients were newly diagnosed with cancer of the trachea, bronchia and lung. The age-standardised[1] incidence rate was 68.0/100,000 in men and 48.8/100,000 in women [4].
- BRAF mutations are detected in 1-2% of all patients with NSCLC. About half of these are V600 mutations, the vast majority of which are V600E, rarely V600G [5].

Current treatment [5]

- The following information regarding the treatment of NSCLC with BRAF V600 is available from Onkopedia:
  - In previously untreated patients, the BRAF inhibitor dabrafenib resulted in a remission rate of 64% and a median overall survival of 24.6 months in a single-arm phase II study in combination with the MEK inhibitor trametinib.
  - In patients pretreated with chemotherapy, the remission rate was 63%.
  - In indirect comparison, the rate of severe adverse events is lower than with chemotherapy. Data from randomised trials are not available.
  - Dabrafenib/trametinib can be used in first- or second-line therapy for BRAFV600 mutations.
  - For other point mutations outside the V600 position, the situation is complex because kinase-inactivating mutations also occur. In this case, a molecular tumour board should be consulted.
  - Direct comparisons versus immunochemotherapy are not available.
  - Tumours with BRAF V600E may respond to immunotherapy, so chemo-immunotherapy is also a reasonable option.

Regulatory status

EMA [2, 3]	FDA [6-8]
Braftovi®	**Braftovi®**
Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Braftovi®. The CHMP adopted a new indication as follows: ❖ Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation. **Other indications:** ❖ Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	**Approval status for this indication**: On 11 October 2023, the FDA approved encorafenib (Braftovi®) with binimetinib (Mektovi®) for adult patients with metastatic NSCLC with a BRAF V600E mutation, as detected by an FDA-approved test. The FDA also approved the FoundationOne CDx (tissue) and FoundationOne Liquid CDx (plasma) as companion diagnostics for encorafenib with binimetinib. **Other indications**: Braftovi® is indicated ❖ in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

[1] European Standard Population 2013.

❖ Encorafenib in combination with cetuximab, is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy **Mektovi®** **Approval status for this indication**: On 25 July 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Mektovi®. The CHMP adopted a new indication as follows: ❖ Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation. **Other indications:** ❖ Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	❖ in combination with cetuximab, for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy. **Mektovi®** **Approval status for this indication**: On 11 October 2023, the FDA approved encorafenib (Braftovi®) with binimetinib (Mektovi®) for adult patients with metastatic NSCLC with a BRAF V600E mutation, as detected by an FDA-approved test. The FDA also approved the FoundationOne CDx (tissue) and FoundationOne Liquid CDx (plasma) as companion diagnostics for encorafenib with binimetinib. **Other indications:** Mektovi® is indicated ❖ in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Manufacturer

Braftovi® and Mektovi® are manufactured by Pierre Fabre.

Costs [9]

28 Braftovi® hard capsules 50 mg = € 447.44 (ex-factory price)
84 Mektovi® film tablets 15 mg = € 2,013.46 (ex-factory price)

Warnings and precautions[2] [7, 8]

Braftovi®

- **New primary malignancies, cutaneous and non-cutaneous**
  - Can occur. Monitor for malignancies and perform dermatologic evaluations before, while on therapy, and following treatment discontinuation.
- **Tumour promotion in BRAF wild-type tumours**
  - Increased cell proliferation can occur with BRAF inhibitors.
- **Cardiomyopathy**
  - Assess left ventricular ejection fraction (LVEF) before initiating treatment with Braftovi® and binimetinib, and after one month of treatment, then every 2 to 3 months thereafter. The safety of Braftovi® in combination with binimetinib has not been established in patients with LVEF below 50%.
- **Hepatotoxicity**
  - Monitor liver function tests before and during treatment with Braftovi® and binimetinib and as clinically indicated.
- **Haemorrhage**
  - Major haemorrhagic events can occur in patients receiving Braftovi® and binimetinib.
- **Uveitis**
  - Perform ophthalmologic evaluation at regular intervals and for any visual disturbances.
- **QT prolongation**
  - Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation.

[2] Chapter "Warnings and precautions" refers to the FDA label information.

- Withhold Braftovi® for QTc of 500 ms or greater.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm. Advise females with reproductive potential of potential risk to the foetus and to use effective non-hormonal method of contraception.

❖ **Risks associated with Braftovi® as a single agent**
- If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of Braftovi® as recommended.

❖ **Risks associated with combination treatment**
- Braftovi® is indicated for use as part of a regimen in combination with binimetinib or cetuximab.

Mektovi®

❖ **New primary malignancies, cutaneous and non-cutaneous**
- Can occur when Mektovi® is used in combination with encorafenib. Monitor patients for new malignancies prior to initiation of treatment, during treatment, and after discontinuation of treatment.

❖ **Cardiomyopathy**
- Assess LVEF before initiating treatment, after one month of treatment, then every 2 to 3 months thereafter. The safety of Mektovi® has not been established in patients with LVEF below 50%.

❖ **Venous thromboembolism**
- Deep vein thrombosis and pulmonary embolism can occur.

❖ **Ocular toxicities**
- Serous retinopathy, retinal vein occlusion and uveitis have occurred. Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances.

❖ **Interstitial lung disease (ILD)**
- Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD.

❖ **Hepatotoxicity**
- Monitor liver function tests before and during treatment with Mektovi® and encorafenib and as clinically indicated.

❖ **Rhabdomyolysis**
- Monitor creatine phosphokinase and creatinine periodically and as clinically indicated.

❖ **Haemorrhage**
- Major haemorrhagic events can occur in patients receiving Mektovi® and encorafenib.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm. Advise females with reproductive potential of potential risk to the foetus and to use effective contraception.

Study characteristics [1, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
PHAROS NCT03915951	98[3]	oral encorafenib 450 mg once daily + binimetinib 45 mg twice daily in 28-day cycles	-	ORR by IRR	NA	ongoing[4], open-label, single-arm, phase II study	-	Pfizer	PHAROS [1]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (n=98)
❖ Written informed consent ❖ Age ≥ 18 years	❖ Patients who have documentation of any of the following: EGFR mutation, ALK fusion oncogene or ROS1 rearrangement. ❖ More than 1 prior line of systemic therapy in the advanced/metastatic setting.	❖ Median age, (range): 70 (47-86) ❖ Male sex: 47% ❖ Ethnicity:

[3] 59 patients were treatment-naive and 39 patients were previously treated.
[4] Estimated study completion date is 12/2024.
[5] For detailed in-and exclusion criteria, please see trial protocol.

❖ Histologically confirmed diagnosis of NSCLC that is currently Stage IV (M1a M1b, M1c- AJCC 8th edition). ❖ Presence of a BRAFV600E mutation tumour tissue or blood as determined by a local laboratory assay. ❖ Prior to enrollment, the investigator must obtain adequate tumour tissue for submission to a central laboratory for confirmation of BRAFV600 mutation status. ❖ Patients who are either treatment-naïve, OR who have received • first-line platinum-based chemotherapy OR • First-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy. ❖ Presence of measurable disease based on RECIST v1.1. ❖ ECOG performance status of 0 or 1. ❖ Adequate bone marrow function is characterised by the following at screening: • ANC ≥ 1.5 × 109/L; • Platelets ≥ 100 × 109/L; • Haemoglobin ≥ 8.5 g/dL ❖ Adequate hepatic and renal function characterised by the following at screening: • Total bilirubin ≤ 1.5 × ULN • ALT and AST ≤ 2.5 × ULN, or ≤ 5 × ULN in presence of liver metastases; • Serum creatinine ≤ 1.5 × ULN; or calculated creatinine clearance ≥ 50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m2. ❖ Able to swallow, retain and absorb oral medications. ❖ Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.	❖ Previous treatment with any BRAF inhibitor or MEK inhibitor prior to screening and enrollment. ❖ Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment: • ≤ 14 days for chemotherapy, targeted small-molecule therapy, radiation therapy, immunotherapy, or antineoplastic biologic therapy. • ≤ 14 days or 5 half-lives (minimum of 14 days) for investigational agents or devices. • Palliative radiation therapy must be complete 7 days prior to the first dose of study treatment. ❖ Major surgery ≤ 6 weeks prior to start of study treatment. ❖ Patient has not recovered to ≤ Grade 1 from toxic effects of prior therapy and/or complications from prior surgical intervention before starting study treatment. ❖ Current use of a prohibited medication, as described in Protocol, or use of a prohibited medication ≤ 1 week prior to the start of study treatment. ❖ Impairment of gastrointestinal function or disease which may significantly alter the absorption of oral study treatment. ❖ Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following: • History of acute myocardial infarction, acute coronary syndromes≤ 6 months prior to start of study treatment. • Congestive heart failure requiring treatment (NYHA Grade ≥ 2); • LVEF < 50% as determined by MUGA or ECHO. • Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite optimal therapy. • Clinically significant cardiac arrhythmias. • Triplicate average baseline QTcF interval ≥ 480 ms or a history of prolonged QT syndrome. ❖ History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to the first dose of study treatment. ❖ History or current evidence of RVO or current risk factors for RVO; history of retinal degenerative disease. ❖ Concurrent neuromuscular disorder that is associated with the potential of elevated CK. ❖ Evidence of active noninfectious pneumonitis or history of interstitial lung disease. ❖ Evidence of HBV or HCV infection. ❖ Known history of a positive test for HIV or known AIDS. ❖ Active infection requiring systemic therapy.	• White: 88% • Asian: 7% • Black: 3% • American Indian: 1% • Unknown: 1% ❖ ECOG PS: • 0: 27% • 1: 73% ❖ Smoking status • Current: 13% • Former: 57% • Never: 30% ❖ BRAF V600 status • V600E: 100% • V600D: 1% (comutation with V600E) ❖ Method of local BRAF testing • PCR: 26% • Tissue NGS: 72% • Plasma NGS: 1% ❖ Tumour histology • Adenocarcinoma: 97% • Squamous cell carcinoma: 2% • Other: 1% ❖ Brain metastases • No: 92% • Yes: 8% ❖ Prior systemic treatment for metastatic disease: 40% • Immunotherapy: 24% o Monotherapy PD-(L)1: 12% o Combination PD-(L)1: 12% • Chemotherapy: 18% ❖ Prior radiotherapy: • No: 73% • Yes: 27%

❖ Female patients of childbearing potential as described in Appendix, must have a negative serum βHCG test result. ❖ Female patients of childbearing potential must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix, and to not donate ova from Screening until 30 days after the last dose of study treatment. ❖ Male patients must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix 1, and to not donate sperm from Screening until 90 days after the last dose of study drug.	❖ Patients with symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases. ❖ Concurrent or previous other malignancy within 2 years of study entry, except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease and Gleason ≤ 6 prostate cancer. ❖ Known sensitivity or contraindication to any component of study treatment (binimetinib and encorafenib), or their excipients. ❖ Pregnancy or breastfeeding or patients who plan to become pregnant during the duration of the study. ❖ Other severe, acute or chronic medical or psychiatric condition(s) or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.	

Efficacy	**Safety** (n=98)
Data cutoff 22 September 2022 **Treatment-naïve patients:** **ORR by IRR**: 75% (95% CI, 62-85); **CR**: n=9; **PR**: n=35 **Median time to response**: 1.9 months (range, 1.1-19.1) **Median DOR by IRR**: NE (95% CI, 23.1-NE) **Durable responses lasting ≥12 months**: 59% **DCR after 24 weeks**: 64% (95% CI, 51-76) **Median duration of follow-up for PFS by IRR**: 18.2 months (95% CI, 16.4-22.3) **Median PFS by IRR**: NE (95% CI, 15.7-NE) **Deaths at the time of data cutoff**: 29% **Median OS**: NE **Previously treated patients:** **ORR:** 46% (95% CI, 30-63); CR: n=4; PR: n=14 **Median time to response by IRR**: 1.7 months (range,1.2-7.3) **Median DOR by IRR:** 16.7 months (95% CI, 7.4-NE) **Durable responses lasting ≥12 months:** 33% **DCR after 24 weeks**: 41% (95% CI, 26-58) **Median duration of follow-up for PFS by IRR:** 12.8 months (95% CI, 9.0-19.8) **Median PFS by IRR:** 9.3months (95%CI, 6.2-NE) **Deaths at the time of data cutoff**: 33%	**All-causality AEs:** 99% **TRAEs of any grade**: 94% **TRAEs grade** 38% **TRAEs grade 4:** 3% **TRAEs leading to permanent:** 15% **Serious TRAEs:** 14% **Deaths:** 31%[6]

[6] The primary reasons for death were disease progression (24%), AE (2%), or other causes (4%). One patient died due to intracranial haemorrhage, which was assessed as treatment related by the investigator.

Median OS: NE	

Patient-reported outcomes

Evaluation of patient-reported outcomes is not provided in PHAROS trial.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 46%	-	ORR ≥20%-<60% AND DoR ≥9 months	3	-	-	-	3

The adapted ESMO-MCBS scale was not applied due to the low level of evidence (single-arm study).

Risk of bias - study level (case series) [12]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no	yes	yes	unclear[7]	yes

Overall risk of bias: moderate

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT03915951 / PHAROS	Please see above.	12/2024
NCT05195632 / OCEANII	Open-label, phase 2 Study with a safety lead-in part investigating the efficacy, safety and pharmacokinetics of encorafenib and binimetinib combination in BRAF V600E mutated Chinese patients with metastatic NSCLC who are BRAF- and MEK inhibitor treatment-naïve.	05/2025
NCT04526782 / ENCO-BRAF	Phase 2 Study of the BRAF inhibitor encorafenib in combination with the MEK inhibitor binimetinib in patients with BRAFV600E-mutant metastatic NSCLC.	03/2026

Available assessments

- In April 2023, NIHR published a Health Technology Briefing "Encorafenib with binimetinib for treating metastatic BRAF V600 mutant non-small-cell lung cancer" [14].
- No further assessments were identified via ICER, NICE, CDA-AMC and G-BA.

[7] The trial is currently ongoing.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a new indication** for binimetinib (Mektovi®) in combination with encorafenib (Braftovi®) for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation. In October 2023, the **FDA approved** Braftovi® with Mektovi® for adult patients with metastatic NSCLC with a BRAF V600E mutation, as detected by an FDA-approved test.
- **PHAROS (NCT03915951)** is an **ongoing**, open-label, **single-arm, phase II study** evaluating the efficacy and safety of encorafenib plus binimetinib in patients with BRAFV600E-mutant metastatic NSCLC. Patients aged ≥18 years with histologically confirmed stage IV or recurrent NSCLC, measurable disease on the basis of RECIST 1.1, and an ECOG PS of 0 or 1 were included in the study. Patients who had prior treatment with a BRAF or MEK inhibitor, other driver alterations, untreated symptomatic brain metastasis, or leptomeningeal disease were excluded.
- The primary endpoint was confirmed **ORR by IRR**. In treatment-naïve patients, ORR by IRR was 75% (95% CI, 62-85) and in previously treated patients 46% (95% CI, 30-63).
- Patient-reported outcomes are not evaluated in PHAROS trial.
- The original **ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of **3**. The adapted ESMO-MCBS scale was not applied due to the low level of evidence (single-arm study).
- The **risk of bias** was considered **moderate**.
- Besides PHAROS, two further ongoing phase 2 trials were identified, assessing the combination of encorafenib and binimetinib in patients with BRAF V600E-mutant NSCLC.
- More robust data is required to determine the role of the assessed treatment option for patients with advanced NSCLC with a BRAF V600E mutation. This includes final analysis data from the PHAROS trial, additional phase 3 data and, not least, patient-reported outcome data.

First published: 08/2024

Abbreviations: AE=adverse event, AIDS=acquired immunodeficiency syndrome, AJ=adjustment, AJCC=American Joint Committee on Cancer, ALK=anaplastic lymphoma kinase, ALT=alanine aminotransferase, ANC=absolute neutrophil count,AST=aspartate aminotransferase, BRAF=v-Raf murine sarcoma viral oncogene homolog B, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, DOR=duration of response, ECHO=echocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV= human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstitial lung disease, Int.=intention, IRR=independent radiology review, LVEF=left ventricular ejection fraction, MEK=mitogen-activated protein kinase MG=median gain, MUGA=multi-gated acquisition, n=number of patients, NA=not available, NE=not evaluable, NGS=next-generation sequencing, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, NYHA= New York Heart Association, ORR=objective response rate, OS=overall survival, PCR=polymerase chain reaction, PD-1=programmed cell death protein 1, PD-L1=programmed cell death protein ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse event, ULN=upper limit of normal

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